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FOREWORD

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John L. Young, Jr. 11/15/95
PI - Signature Date

TABLE OF CONTENTS

	<u>Page</u>
Front Cover	1
Report Documentation Page	2
Foreword	3
Introduction	5
Body	5
Conclusions	13
References	13
Appendixes	
I. PDQ: Recommended Treatments for Breast Cancer	14
II. AJCC Staging Categories	74
III. Letter to Physicians	76
IV. Biographical Sketch	79
V. Application to the Committee for the Protection of Human Subjects	81

INTRODUCTION

The purpose of this project is to enhance the value of the California Cancer Registry as a research tool for clinicians and epidemiologists interested in conducting breast cancer research. The California Cancer Registry began statewide population-based coverage on January 1, 1988. Between 1988 and 1993 all breast cancers were staged according to the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program Summary Staging Guide (1), basically a classification of cases into in situ, localized, regional and distant disease. A major objective of this award has been to reclassify all breast cancer cases diagnosed between 1988-93 according to the SEER Program's Extent of Disease (2) classification scheme and to apply a computer program available from the NCI to classify cases into the TNM classifications and the Staging Categories (0,I,II,III,IV) of the American Joint Committee on Cancer (3). This would allow for classification of breast cancer according to all staging schemes currently in use in the United States so that researchers could classify breast cancer cases according to the scheme most useful to their research.

A second objective of this award was to enhance the availability of breast cancer treatment data included in the California Cancer Registry. Detailed and complete treatment data for all breast cancer cases is difficult to ascertain due to the fact that much treatment, especially chemotherapy, is given outside of acute care facilities. The approach has been to compare for individual patients the treatment information currently recorded into the data base to that recommended in the NCI's Patient Data Query (PDQ) data base. For all patients not recorded as having received the recommended treatment, the physician of record is to be queried regarding any additional treatment which the breast cancer patient may have received as a part of her initial course of therapy.

A third objective of the award has been to link the California Cancer Registry breast cancer cases against other available data bases to enhance survival data by updating current vital status of breast cancer patients and to identify groups of women who may be at an increased risk to breast cancer.

BODY

Progress to date:

Objective 1 - Reclassifying Breast Cancer Cases According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program Extent of Disease (EOD) and the American Joint Committee on Cancer (AJCC) Staging schemes.

Stage or extent of disease at the time of initial diagnosis is currently felt to be the most important prognostic factor available to plan an appropriate course of treatment for breast cancer patients. Further, stage of disease is important in accessing programs to detect breast cancer at earlier stages when the disease is more curable. There are multiple schemes available to categorize patients according to their stage at diagnosis. Each of these schemes is suited to measuring a particular aspect of disease. For example, the scheme of classifying patients according to categories of in situ, localized, regional, and distant disease was introduced by the National Cancer Institute in the early

1950s and has been in continuous use since that time. This scheme, therefore, is useful in examining time trends and in determining the impact of screening programs. Using data classified according to this "summary staging scheme" one can see the impact that wide-spread use of screening mammography has had on detecting disease at earlier stages. For example, Figure 1 shows a trend in earlier stage diagnosis for breast cancer in the San Francisco Bay Area for the time period 1980-1993, and Figure 2 shows the change in early stage breast cancer diagnoses for all ten regions of the California Cancer Registry between 1988 and 1993.

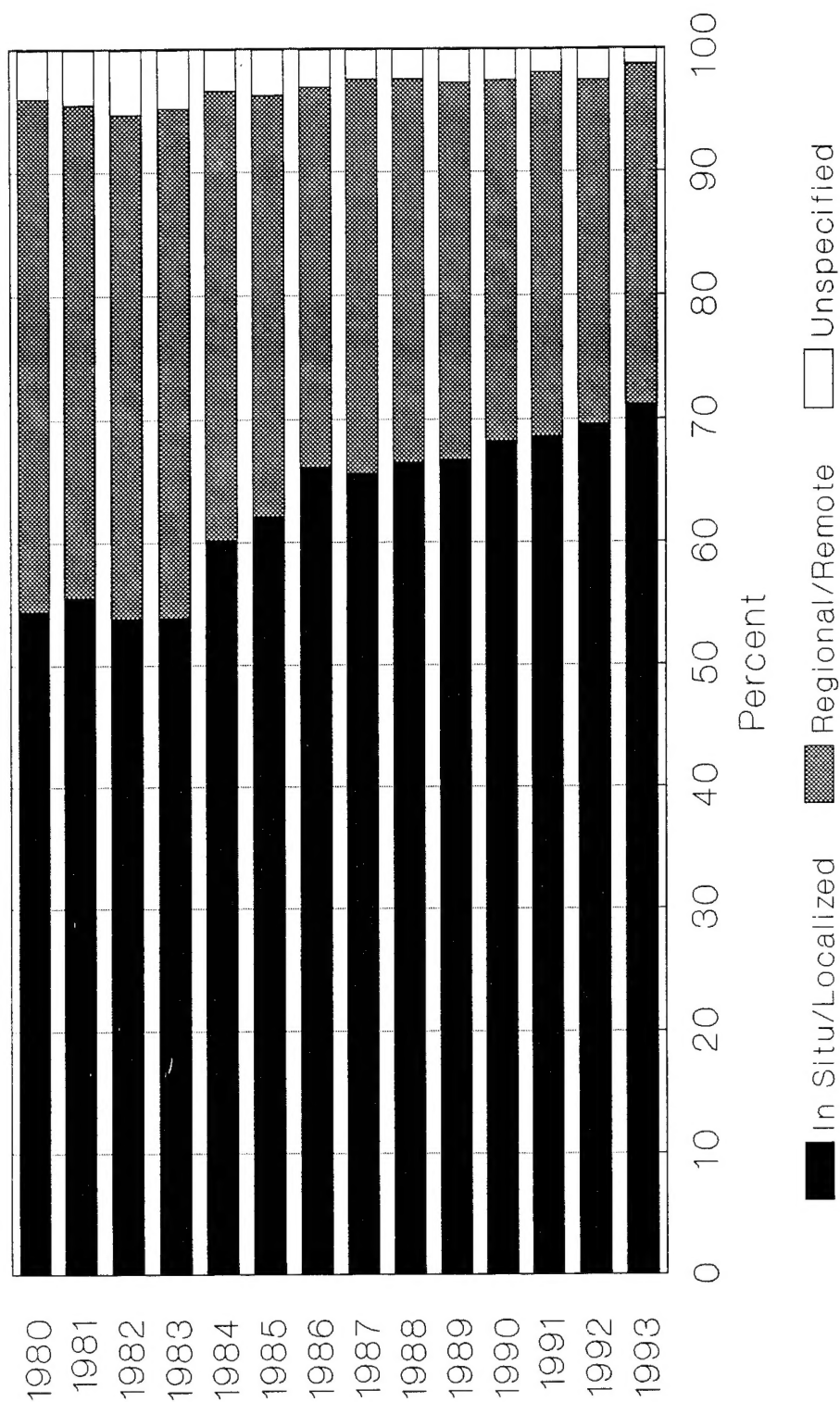
This historical classification, however, is not particularly useful in treatment planning, since the more detailed staging categories of the American Joint Committee on Cancer (AJCC) based on size of tumor and lymph node involvement are preferred by treatments. Fortunately, the SEER Program has developed a classification scheme, referred to as extent of disease (EOD) at diagnosis, which allows for the collection of detailed data on size of tumor, extension of tumor, and lymph node involvement which will allow the collapse of data into either scheme. The major objective of this procurement has been to reclassify the California Cancer Registry's backlog of cases according to SEER EOD and then into AJCC staging categories.

Between January 1, 1988 and December 31, 1993 there were 118,308 female California residents diagnosed with breast cancer. Of these cases, 17,862 had previously been classified according to the SEER Program's extent of disease (EOD) coding schemes due to the participation of the San Francisco Bay area in the SEER Program itself. Thus, 100,446 cases needed to be coded and classified according to this scheme. Coding according to the SEER EOD scheme became mandatory beginning with January 1, 1994 cases throughout California. However, there have been only a limited number of experienced Certified Tumor Registrars (CTRs) available to code the historical records of breast cancer cases.

For purposes of cancer reporting, the State of California and its 31.7 million population has been divided into 10 distinct geographic regions ranging in population from 1.4 million in the Northern Sierra Region (a 16-county area) to a population of 9.2 million in the single-county reporting area of Los Angeles. Table 1 shows the number of female breast cancer cases by region and year of diagnosis. Entries which are shaded denote the years for which the coding of SEER EOD has now been completed. Both the money awarded and the availability of experienced coders have not been sufficient to complete the coding of the entire historical data base during Year 01 of this award. As can be seen from the table, first priority was given to 1993 cases and working backward through to 1988. Additional funding to assist in coding this backlog has become available through a special tax imposed on cigarettes. Trained staff have worked overtime, part time staff have been increased to full time and private vendors have been utilized in attempt to code the entire historical file in a timely manner. It is estimated that the entire file will be completed by June 30, 1996. We have also received the computerized conversions software program from the NCI which uses the EOD coding to classify breast cancer cases into the AJCC TNM and Staging Categories. This conversion program will be applied to the data file when the EOD coding task is complete.

Figure 1

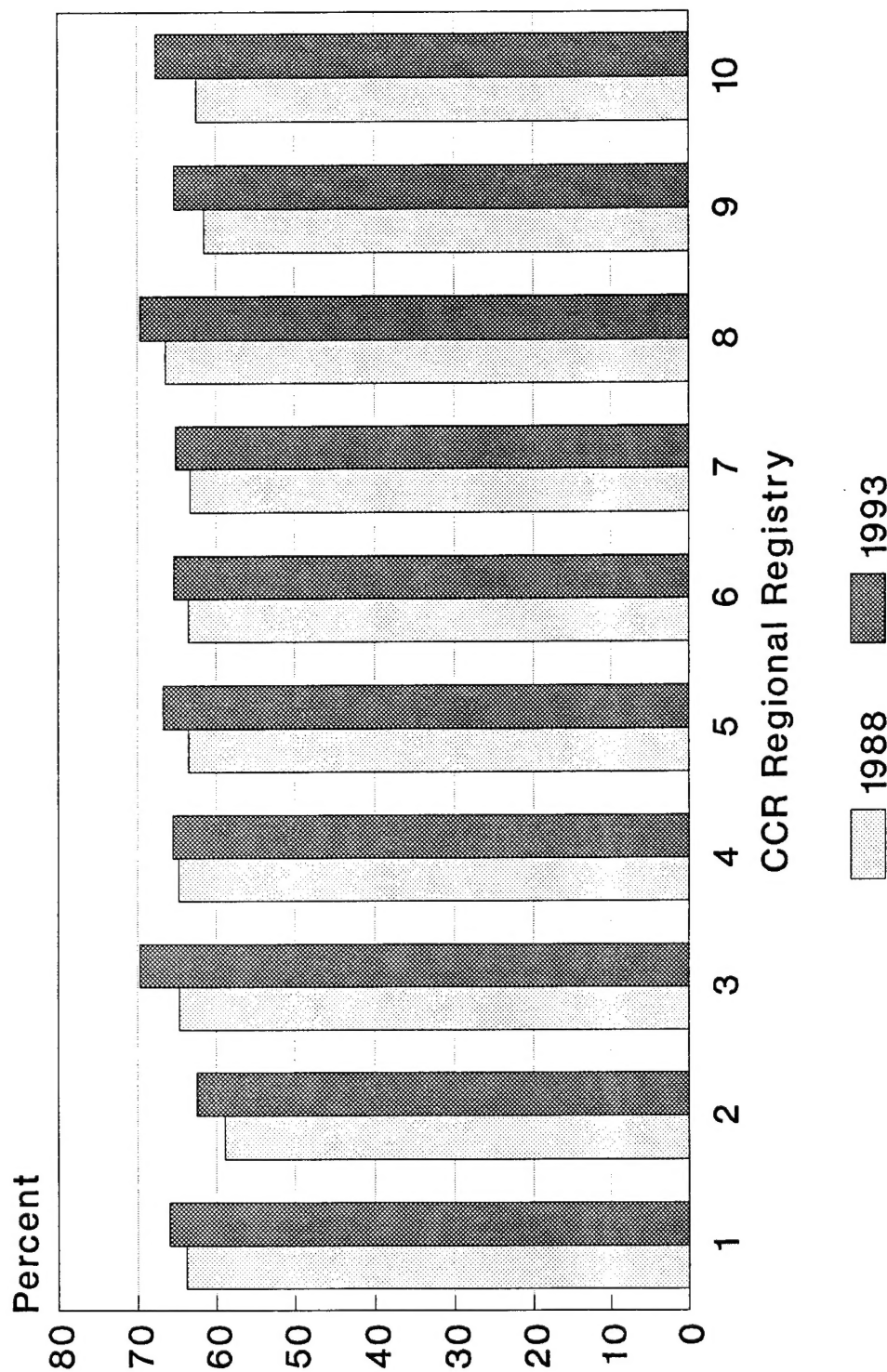
FEMALE BREAST CANCER STAGE AT DIAGNOSIS SAN FRANCISCO BAY AREA, 1980 - 1993



Source: California Cancer Registry, Region 8.

Figure 2

Percent of Female Breast Cancers Diagnosed as Early Stage Tumors, California, 1988 and 1993



Early stage = in situ or localized tumors, no lymph node involvement.
Source: California Cancer Registry, 10/95.

TABLE 1
Breast Cancer Cases, 1988-1993
By Region, Invasive and Insitu

Breast (26000)	Year of Diagnosis (YY)					
	1988	1989	1990	1991	1992	1993
Region ID						
1	1,279	1,315	1,289	1,398	1,412	1,411
2	1,174	1,107	1,320	1,363	1,352	1,368
3	1,743	1,692	1,817	1,892	1,977	1,851
4	832	787	856	891	907	919
5	1,469	1,439	1,655	1,682	1,665	1,755
6	973	953	990	1,086	1,152	1,070
7	1,540	1,587	1,752	1,866	1,939	1,841
8	2,894	2,860	2,995	3,016	3,105	2,992
9	5,503	5,190	5,305	5,247	5,495	5,303
10	1,612	1,528	1,665	1,647	1,808	1,777
Total	19,019	18,458	19,644	20,088	20,812	20,287

Objective 2: Enhancing the Availability of Cancer Treatment Data in the California Cancer Registry

Until recently, most population-based registries outside the SEER Program network have been incidence only registries and have not been concerned with the collection of treatment data. Since its inception, the California Cancer Registry has recorded the first course of cancer treatment for all patients. Unfortunately, the data are known to be incomplete, especially for those cancer sites such as breast cancer which are traditionally treated with a first course of chemotherapy. Chemotherapy is primarily given outside the acute care hospital setting, and medical records often lack the details of the full course of therapy being given.

Standard/recommended/state-of-the-art treatment for each stage and type of breast cancer is included in the NCI's Physician Data Query (PDQ) system available to all practicing physicians with access to a computer terminal. Naturally, not all physicians utilize the capabilities of PDQ, and some physicians, hopefully a minority, do not feel that it is appropriate for NCI to "dictate" how patients should be treated, believing that choice belongs to the individual physician. Nevertheless, the yardstick against which state-of-the-art treatment will be measured under this award is the PDQ data base. A complete listing of recommended treatments for breast cancer is included in Appendix I. A computerized program has been developed by the Seattle SEER Program located at the Fred Hutchinson Cancer Research Center to compare cancer treatment data recommended versus that recorded in a cancer registry for 22 groups of patients classified according to AJCC staging categories. These 22 groups are defined in Appendix II. This program has been made available to the California Cancer Registry and its Regional Cancer Registries.

Table 2 shows the results of applying the software program developed in Seattle against the data base for the San Francisco/Oakland Region (California Region 8) which also participates in the SEER Program. This region was selected to be the pilot region since it has routinely applied all treatment data which may have been sent in on "correction" records by local hospital registrars who discovered additional treatment data in the process of patient follow-up. Amazingly, 68% of breast cancers did not receive the full course of treatment recommended by the PDQ system. Preliminary examination of data in the San Jose and Orange County Regions have revealed similar results. Obviously, available funding will not allow for the contact of physicians for the entire patient population not receiving the recommended treatment. Therefore, first priority will be given to women with early stage disease, i.e. AJCC Stages 0, I, and IIA (patient groups 1- 10 in Table 2). A copy of the intended letter to physicians is included as Appendix III. It is anticipated that 1994 incidence data will be complete by January of 1996 at which time these same groups of patients will be identified for 1994 diagnoses. Routine follow-back to physicians will be initiated as quickly as possible and will continue throughout the duration of this award.

TABLE 2
1993 Breast Cases
Summary of All Groups

	All Cases Checked	Cases With Complete Treatment	Cases with Incomplete Treatment
Group 1	595	352	243
Group 2	61	57	4
Group 3	325	110	215
Group 4	1,207	485	722
Group 5	527	2	525
Group 6	247	59	188
Group 7	510	91	419
Group 8	165	88	77
Group 9	315	146	169
Group 10	86	2	84
Group 11	18	4	14
Group 12	112	12	100
Group 13	262	30	232
Group 14	2	0	2
Group 15	8	3	5
Group 16	1	1	0
Group 17	2	0	2
Group 18	81	21	60
Group 19	75	15	60
Group 20	12	0	12
Group 21	0	0	0
Group Unknown	3	0	3
TOTALS	4,614	1,478	3,136

Objective 3: Linkage of the California Cancer Registry with Other Data Bases to Enhance Survival Data, Collect Comorbidity Information, and Identify Women at High Risk to Breast Cancer

Utilizing funding from this award, a full-time data linkage expert, Mr. Mark Allen, has been employed. (A brief biographical sketch is included in Appendix IV.) Utilizing AUTOMATCH Software available from a software vendor, Mr. Allen has undertaken a number of linkage activities. The first was a series of internal linkages among the ten regional registries to uncover any cases that received treatment in facilities in the different geographical regions. This activity was undertaken to insure that all relevant first course of treatment information was consolidated into a single cancer record.

The second project involved linkage with Health Care Financing Administration (HCFA) MediCare files. The CCR developed a Memorandum of Understanding with the HCFA to exchange information on our files for women 65 years of age and older. This past year, the HCFA sent the CCR a file of names and identifying information on 4,830 women treated in California inpatient hospitals and 2,510 women treated in California outpatient facilities for breast cancer in 1993. These records were linked to 128,968 breast cancer records with date of diagnosis 1988-1993 that were on the CCR file as of August 1995. To date 96.8% of the HCFA inpatient records and 94.2% of the outpatient records matched with the CCR records. Additional work is underway to uncover characteristics of the unmatched group that might have led to their exclusion from the CCR files (e.g., out-of-state residence). Once this has been completed, the next step will be to begin a comparison of treatment information in the HCFA files with that in the CCR files, and to capture morbidity information from the HCFA files for enhancement of the CCR breast cancer research file.

A similar set of activities is planned for linking hospital discharge data for women under the age of 65 and for those over 65 who are not included in MediCare. The Office of Statewide Health Planning and Development collects information on every hospital discharge in the state. Beginning with July 1, 1990 discharges, these reports also contained social security numbers, but this information is confidential. The CCR has applied to the State's Health and Welfare Agency Committee for the Protection of Human Subjects for access to the confidential portion of the State's Hospital Discharge Data File for female breast cancer cases. (Appendix V contains a copy of that application.) Approval is expected by early December. As soon as it is obtained, we will begin the process of linking breast cancer cases with the discharge data to examine any improvement in treatment information and to collect comorbidity information.

The third linkage project involved a pilot test of the feasibility of collecting patient follow-up information by linking breast cancer cases with the Department of Motor Vehicles files. In California, a record is kept for each time a person receives or renews a driver's license, receives a traffic ticket, and receives or renews a vehicle registration. While access to the DMV records is restricted, the CCR has arranged for the DMV to perform an exact match linkage (First Name, Last Name, and Date of Birth) for follow-up purposes, i.e. if there is DMV activity with an individual, it is assumed that individual was alive on the date of the transaction. In September, the CCR sent a pilot test file of 72,123 records from the San Francisco Bay Area Region to the DMV for processing. The linkage yielded a 58% match rate, and 16,920 records or 23.5% of the total had a

follow-up date from DMV that was more recent than the follow-up date contained in the CCR. This process was judged successful for increasing follow-up (and consequently improving survival analyses). During the next year we intend to institute the DMV linkage process to an annual basis for all regions.

A fourth linkage was performed in response to a request from the American Cancer Society (ACS) to conduct a pilot linkage study. In 1982 the ACS enrolled nearly 800,000 volunteers into the Cancer Prevention Study II, an ongoing prospective mortality study. In 1992 and 1993 a nutrition survey was mailed to a subgroup of the cohort and nearly 25,000 members from California responded. After developing appropriate confidentiality safeguards, the CCR linked the 23,489 ACS nutrition survey respondents to the 641,255 tumors diagnosed between 1988 and 1992 that were in the file. This linkage resulted in 1,364 tumors among 1,316 individuals. Of these, 329 or 24.1% were breast cancers. The ACS and the CCR intend to perform this linkage on a periodic basis in the future to assess the predictive ability of nutrition survey data on subsequent breast and other cancer diagnoses.

CONCLUSIONS

This project, after normal startup delays, is catching up to schedule for coding SEER Extent of Disease for and reclassifying to AJCC TNM and Stage. Progress should be on schedule by June 1996. Follow-back to physicians for complete first course of treatment data has been delayed due to the unexpectedly large number of cases that either have incomplete data or where physicians have not applied recommended treatments. As a consequence, the project has had to scale back the proportion of "incomplete" case files that will be contacted. Routine follow-back will be initiated as quickly as possible and will continue throughout the duration of the award. Linkage activities are on schedule, and available resources allowed the project to collaborate on an additional study with the American Cancer Society.

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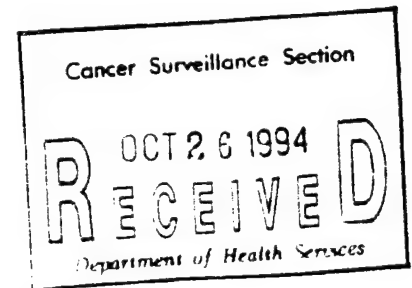
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NORTHERN CALIFORNIA CANCER CENTER

32960 Alvarado-Niles Road, Suite 600, P.O. Box 5033, Union City, CA 94587-3106 • (510) 429-2500 FAX (510) 429-2550

MEMORANDUM

TO: CCR and Regional Registry Directors
FROM: Dee W. West, Ph.D. *[Signature]*
DATE: October 24, 1994
SUBJECT: PDQ Recommended Treatment for Breast Cancer



As promised at the last conference call I asked our CIS Director to obtain information from the PDQ on treatment for breast cancer, especially stage 0 and 1. Attached are statements for these stages as well as the entire PDQ statement for physicians. This is probably more than you ever wanted to know.

I assume the computer program from Seattle has simplified this for our use. We need to wait until John has received this program before we write our definitions and select our cases for follow back to physicians.

Anyway, the attached will give you a general idea of what is recommended, and also what is available from PDQ.

Attachment

DIAGNOSIS #1 OF 1

FRI OCT 21 12:06:35 1994

-----BREAST CANCER-----

TREATMENT OVERVIEW

The choice of state-of-the-art treatment for breast cancer is influenced by tumor stage and ER and PR levels and by patient age and menopausal status. All newly diagnosed patients with breast cancer may appropriately be considered as candidates for one of the numerous ongoing clinical trials designed to improve survival and decrease the morbidity of current conventional treatment.

Reconstructive surgery:

For breast cancer in situ and stage I and II infiltrating cancer, reconstructive surgery may be employed if a mastectomy is performed. It may be done at the time of the mastectomy (immediate reconstruction) or at some subsequent time (delayed reconstruction) in an attempt to restore the anatomical deficit of the mastectomy.[1-4] Breast contour can be restored either by the submuscular insertion of an artificial implant (silicone or saline-filled) or by a rectus muscle or other flap. Both procedures offer satisfactory cosmetic results. Insertion of an artificial implant is a relatively simple procedure. A saline-filled tissue expander can be inserted beneath the pectoral muscle. Saline is used to expand it over a period of weeks or months until the desired volume is obtained. The tissue expander is then replaced by a permanent implant. Rectus muscle flaps, which offer a better cosmetic result, require a considerably more complicated and prolonged operative procedure, and blood transfusions may be required. There is no convincing evidence that a silicone implant induces cancer or autoimmune disease. Problems associated with silicone implants include contracture of the capsule around the implant causing hardening and pain, rupture of the implant with release of the silicone gel, and infection.[5-7] In rare instances, either procedure could make a local recurrence more difficult to detect. Following breast reconstruction, radiotherapy can be delivered to the chest wall and regional nodes either in the adjuvant setting or upon local disease recurrence. Although this does not adversely affect outcome, cosmesis may be affected and the incidence of capsular fibrosis, pain, or the need for implant removal may be increased.[6] The use of silicone implants for breast augmentation may make the early detection of breast cancer more difficult by obscuring and compressing breast parenchyma.[5,7-9] The FDA has announced that silicone breast implants will be available only through controlled clinical studies. Women who wish to undergo reconstructive surgery following mastectomy will be assured access to those studies. However, the FDA has placed no restrictions on the use of saline-filled breast implants, which may constitute a reasonable alternative.

There is no consistent evidence that timing of mastectomy with regard to the menstrual cycle has an impact on either overall or disease-free survival.[10,11]

The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.

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TREATMENT BY STAGE/CELL TYPE BREAST CANCER IN SITU

The articles referenced in this section discussing results of National Surgical Adjuvant Breast and Bowel Project (NSABP) studies may include data from institutions where falsified data have been reported. An indication that a specific article may be affected is included in the reference list at the end of this section.

Carcinoma in situ is classified as either intraductal carcinoma in situ (DCIS) arising from ductal epithelium or lobular carcinoma in situ (LCIS) arising from the epithelium of the lobules.[1] With the increasing use of screening mammography, noninvasive cancers are more frequently diagnosed and now constitute 15-20% of all breast cancers. DCIS usually presents as microcalcifications or as a soft-tissue abnormality. There are several histologic subtypes: micropapillary, papillary, solid, cribriform, and comedocarcinoma. Some evidence suggests that comedocarcinoma may be more aggressive and associated with a higher probability of microinvasion.[2] LCIS is usually an incidental finding when a biopsy is done for some other abnormality. It is considered a marker for the subsequent development of invasive disease rather than a premalignant lesion. Because it may be difficult to distinguish DCIS from atypical hyperplasia and because certain forms of DCIS may be confused with LCIS, it may be helpful to obtain a second histopathologic interpretation of the biopsy specimen.

-- Intraductal carcinoma --

The customary treatment for DCIS has been mastectomy with excision of lymph nodes around the axillary tail of the breast without a formal dissection of level I axillary lymph nodes. This treatment results in a combined local and distant recurrence rate of 1-2%. The role of breast-conserving operations for DCIS is the subject of ongoing prospective randomized clinical trials. Experience with conservative surgery and radiotherapy suggests that it is a reasonable alternative. Breast cancer recurrence rates of 9-21% are seen, and half of these recurrences are invasive carcinomas. Salvage of recurrences with mastectomy is feasible, and survival remains excellent and comparable to upfront mastectomy.[3-8] Intraductal comedocarcinoma may be associated with a higher risk of local recurrence.

Patients with nonpalpable lesions and microcalcifications detected on mammography who are considered for breast-conserving treatment should undergo careful mammographic evaluation prior to biopsy, followed by needle localization biopsy. Specimen radiography should be performed to confirm that

the lesion has been excised and to direct pathologic sampling. A pathologist should give a careful gross description of the excised specimen and should ink the specimen margins before sectioning to facilitate margin evaluation on permanent section. The relation between the calcifications and the lesion and the distance from the tumor to the inked margins of resection should be described. Following biopsy, mammography should be repeated to confirm that all suspicious microcalcifications have been removed. If residual microcalcifications are seen on post-biopsy mammography, the primary site should be re-excised prior to beginning radiotherapy. The choice of treatment when there is margin involvement by tumor is a controversial issue. Frequently, if the original excision reveals positive margins, a re-excision is done. Then, the extent of disease in the re-excision is evaluated and a decision is made as to whether radiotherapy or mastectomy is appropriate. A simultaneous low axillary dissection is not mandatory as positive lymph nodes are rare.[9] Those patients in whom lymph node involvement is documented should be managed as described under stage II. The role of excision alone in intraductal carcinoma is under investigation, as is the role of radiotherapy in the presence of diffuse microcalcifications.[10]

Surgical and radiotherapeutic techniques are extremely important in obtaining an optimal therapeutic result and satisfactory cosmesis. The availability of specialized equipment and radiation oncologists with expertise using these techniques should be considered in the selection of treatment. Radiation side effects that can be minimized with careful attention to technique include: myocardial damage for left-sided breast lesions, radiation pneumonitis, arm edema, brachial plexopathy, and the risk of second malignancies. Sarcomas in the treatment port and secondary leukemias are very rare. One report suggests an increase in contralateral breast cancer for women under the age of 45 who have received radiation. Modern techniques to minimize radiation dose to the contralateral breast should be used to keep the absolute risk as low as possible.[11,12]

Women who opt for radiotherapy for DCIS should be followed carefully with regular mammography and physical examination to detect asynchronous disease in breast tissue remaining in the ipsilateral breast.[13] Women treated with radiotherapy or mastectomy should also have regular physical and mammographic examinations of the contralateral breast because of the risk of a second primary.

-- Lobular carcinoma in situ --

LCIS is a controversial term; some prefer to call this lesion "lobular neoplasia." The lesion is generally widely distributed throughout the breast and is frequently bilateral. It is considered a marker for the subsequent development of invasive disease rather than a pre-malignant lesion. The patient with LCIS has a 25% chance of developing an invasive cancer (either lobular or, more commonly, infiltrating duct cancer) in either breast within 25 years. The incidence of subsequent cancer is not related to the extent of focal areas of LCIS within the breast. The clinical management of the patient with LCIS is controversial; options include no treatment after biopsy with careful follow-up (physical examination and mammography) or bilateral prophylactic mastectomies. Axillary lymph node dissection is not necessary for the in situ lesion. Many physicians favor periodic examination and mammography without therapy, provided the patient is aware of the risk of developing invasive cancer and is also aware of the possibility of developing metastatic cancer before a clinical diagnosis is established.[14,15] Patients who have undergone local excision for LCIS are eligible for a large multicenter clinical trial of tamoxifen to prevent development of invasive cancer.[16]

Treatment options for intraductal carcinoma (DCIS):[3-6,17,18]

Standard:

1. Total mastectomy.
2. Excisional biopsy with radiotherapy.

Under clinical evaluation:

Segmental/wedge/partial breast resection.

Treatment options for lobular carcinoma in situ (LCIS):[19-21]

Standard:

1. Long-term periodic examination and follow-up after biopsy without further therapy.
2. Bilateral total mastectomy with or without low axillary dissection.

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DIAGNOSIS #1 OF 1

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-----BREAST CANCER-----
TREATMENT OVERVIEW

The choice of state-of-the-art treatment for breast cancer is influenced by tumor stage and ER and PR levels and by patient age and menopausal status. All newly diagnosed patients with breast cancer may appropriately be considered as candidates for one of the numerous ongoing clinical trials designed to improve survival and decrease the morbidity of current conventional treatment.

Reconstructive surgery:

For breast cancer in situ and stage I and II infiltrating cancer, reconstructive surgery may be employed if a mastectomy is performed. It may be done at the time of the mastectomy (immediate reconstruction) or at some subsequent time (delayed reconstruction) in an attempt to restore the anatomical deficit of the mastectomy.[1-4] Breast contour can be restored either by the submuscular insertion of an artificial implant (silicone or saline-filled) or by a rectus muscle or other flap. Both procedures offer satisfactory cosmetic results. Insertion of an artificial implant is a relatively simple procedure. A saline-filled tissue expander can be inserted beneath the pectoral muscle. Saline is used to expand it over a period of weeks or months until the desired volume is obtained. The tissue expander is then replaced by a permanent implant. Rectus muscle flaps, which offer a better cosmetic result, require a considerably more complicated and prolonged operative procedure, and blood transfusions may be required. There is no convincing evidence that a silicone implant induces cancer or autoimmune disease. Problems associated with silicone implants include contracture of the capsule around the implant causing hardening and pain, rupture of the implant with release of the silicone gel, and infection.[5-7] In rare instances, either procedure could make a local recurrence more difficult to detect. Following breast reconstruction, radiotherapy can be delivered to the chest wall and regional nodes either in the adjuvant setting or upon local disease recurrence. Although this does not adversely affect outcome, cosmesis may be affected and the incidence of capsular fibrosis, pain, or the need for implant removal may be increased.[6] The use of silicone implants for breast augmentation may make the early detection of breast cancer more difficult by obscuring and compressing breast parenchyma.[5,7-9] The FDA has announced that silicone breast implants will be available only through controlled clinical studies. Women who wish to undergo reconstructive surgery following mastectomy will be assured access to those studies. However, the FDA has placed no restrictions on the use of saline-filled breast implants, which may constitute a reasonable alternative.

There is no consistent evidence that timing of mastectomy with regard to the menstrual cycle has an impact on either overall or disease-free survival.[10,11]

The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.

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TREATMENT BY STAGE/CELL TYPE

STAGE I BREAST CANCER

The articles referenced in this section discussing results of National Surgical Adjuvant Breast and Bowel Project (NSABP) studies may include data from institutions where falsified data have been reported. An indication that a specific article may be affected is included in the reference list at the end of this section.

Stage I breast cancer is often curable with a variety of surgical procedures. However, 10-20 year follow-up of patients managed with surgery alone now reveals that as many as 21% may ultimately relapse.[1] Surgical procedures that conserve a major portion of the involved breast, followed by radiotherapy, provides tumor control equivalent to more extensive surgical procedures. The diagnostic biopsy and the surgical procedure that will be used as initial treatment are often performed as two separate procedures. After the presence of a malignancy is confirmed and the histology is determined, treatment options should be discussed with the patient before definitive therapy is recommended. ER and PR status should be determined for the primary tumor.[2]

In many cases, the diagnosis of breast carcinoma using fine needle aspiration cytology may be sufficient to confirm malignancy. It is then appropriate to discuss the therapeutic options to help the patient with the treatment decision. The surgeon may then proceed with a single, sequential procedure that includes biopsy, frozen section confirmation of carcinoma, and the surgery elected by the patient.

Surgical options include mastectomy, mastectomy with reconstruction, or conservative surgery (i.e., lumpectomy) plus radiotherapy (CS plus RT). Survival is equivalent with any of these options.[3-6] One of the major randomized trials comparing mastectomy to CS plus RT included data from an institution where falsified data have been documented.[3] Preliminary reanalysis of the study excluding all cases from this institution has been performed by the NSABP and the National Cancer Institute and there is no change in the conclusion from the trial, that CS plus RT is equivalent to mastectomy in overall survival. The preliminary reanalysis is available on CancerFax, CancerNet, and in PDQ News. A complete, formal analysis is underway and will be published as soon as possible. Selection of the appropriate therapeutic approach depends on the location and size of the lesion, breast size, appearance of the mammogram, and how the patient feels about preservation of the breast. An axillary lymph node dissection should be performed for histologic study since approximately one-third of patients with

clinically negative nodes will have histologic involvement and would be candidates for additional treatment as per stage II with positive axillary nodes. Although most authorities agree that an axillary node dissection in the presence of clinically negative nodes is a necessary staging procedure, controversy exists as to the extent of the procedure because of long-term morbidity (arm discomfort and swelling) associated with an axillary node dissection. Whether entire areas of potentially lymph-node-bearing tissue should be removed or whether staging can be accomplished by excision of a specific number of nodes is questioned. Recent evidence indicates that removal of five to ten nodes is a satisfactory staging procedure in patients with stage I disease.[7] Data also suggest that the level of lymph node involvement (I vs II vs III) does not add independent prognostic information to the total number of positive axillary nodes.[8] In addition, ER status, tumor size, and measures of proliferative capacity (thymidine labeling index, flow cytometry for measurement of S-phase and ploidy) are highly predictive for risk of relapse in the node-negative patient.[1,9,10] Some patients with stage I tumors appear to be at low risk of relapse (for example, those with tumor size less than 1.0 cm or with more favorable histologic tumor types, e.g., medullary, mucinous, papillary, tubular) and may not require postoperative adjuvant hormonal therapy or chemotherapy.[11-13] High histologic grade of tumor and high rate of mitosis may identify a high-risk subset of patients with T1 lesions less than 1.0 cm.[14] A recent review of 20 years' experience illustrates the prognostic significance of tumor size and histologic grade in stage I tumors.[15]

-- Adjuvant therapy --

Because a significant number of patients with node-negative breast cancer ultimately have disease recurrence, several prospective randomized trials have studied adjuvant chemotherapy or hormonal therapy in node-negative breast cancer. Early trials using tamoxifen, including the Nolvadex Adjuvant Trial Organization (NATO) trial [16] and the Scottish trial,[17] suggested disease-free and overall survival benefit for node-negative patients but data were inconclusive. A small randomized trial comparing adjuvant chemotherapy with CMF versus no adjuvant therapy demonstrated improved disease-free and overall survival for poor-prognosis node-negative patients treated with CMF.[18,19]

Recently, two large trials by the NSABP have demonstrated significant improvement in disease-free survival after five years of follow-up for ER-negative patients treated with adjuvant chemotherapy (methotrexate, fluorouracil, and leucovorin)[20] and for ER-positive patients treated with adjuvant tamoxifen.[21] These trials included data from an institution where falsified data have been documented. Preliminary reanalysis of the study excluding all cases from this institution has been performed by the NSABP and the National Cancer Institute and there is no change in the conclusions from the trials, that overall survival is improved with adjuvant therapy. The preliminary reanalysis of these trials is available on CancerFax, CancerNet, and in PDQ News. A complete, formal analysis is underway and will be published as soon as possible. Both of these large randomized trials demonstrate an early significant benefit for adjuvant therapy in these groups of node-negative breast cancer patients. In both studies, pre- and postmenopausal patients benefitted. An improvement in overall survival has been demonstrated at five years in postmenopausal ER-negative women treated with chemotherapy.[22] These trials, coupled with the three earlier trials and another intergroup adjuvant chemotherapy trial (INT-0011), demonstrated the efficacy of adjuvant treatment. At least five to ten years of further follow-up will be necessary to make a complete assessment of the impact of these therapies.[23-25]

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a

meta-analysis of systemic treatment for early breast cancer by hormonal, cytotoxic, or biologic therapy methods in randomized trials involving 75,000 women with stage I or II carcinoma who were pre- or postmenopausal. In stage I and II postmenopausal women who were ER-positive, tamoxifen at 20 mg daily for at least 2 years (or perhaps longer) was found to prevent recurrent disease and increase survival, with the benefits of initial treatment persisting up to 10 years. Some evidence indicates that ER-negative women could receive similar benefits with tamoxifen treatment. There is a decreased incidence of carcinoma in the contralateral breast and decreased cardiovascular mortality in women treated with tamoxifen. Cytotoxic chemotherapy in the EBCTCG, usually with CMF for 6-12 months, was shown to decrease recurrences and increase survival in both pre- and postmenopausal women with stages I and II disease. The role of ovarian ablation in women under the age of 50 was also analyzed. It was found to produce a survival benefit comparable to that seen with chemotherapy in premenopausal women. This has raised the question again of whether a portion of the impact of systemic chemotherapy is through an endocrine mechanism - ovarian ablation. Such a mechanism of action has been postulated in other trials. In one study, a 12-week chemotherapy regimen induced menopause less frequently than a 36-week regimen and was associated with poorer survival.[26] An additional data-derived analysis of ovarian ablation and chemotherapy postulated an additive effect. The EBCTCG also postulated that there would be an additive effect of tamoxifen and cytotoxic chemotherapy in postmenopausal women.[27,28]

The use of adjuvant tamoxifen has been associated with certain toxicities. The most significant is the development of uterine cancer which, in large clinical trials, has been reported to occur in women treated (2 to 4 times the predicted incidence for untreated women).[29-32] Because of this, patients on tamoxifen should be followed with pelvic exams and have follow-up of all extramenstrual uterine bleeding. Thromboembolic phenomena occurred with an increased frequency of approximately 1% in women on tamoxifen in the NSABP trial.[22] Clotting factor changes have been reported in controlled studies of prolonged tamoxifen use at standard doses; antithrombin III, fibrinogen, and platelet counts have been minimally reduced in patients receiving tamoxifen. The relationship of these counts to thromboembolic phenomena is not clear.[33] Patients should be watched for this complication. Short-term toxicities of tamoxifen in postmenopausal women may include vasomotor symptoms and gynecologic symptoms (vaginal discharge or irritation).[34] The use of clonidine can ameliorate hot flashes in some patients.[35] Tamoxifen therapy may also be associated with certain beneficial estrogenic effects including decreased total and low-density lipoprotein levels.[36,37] A large controlled Swedish trial has shown a decreased incidence of cardiac disease in postmenopausal women taking tamoxifen. Results were better for women taking tamoxifen for five years than in those taking it for two years.[38] A controlled study recently associated long-term tamoxifen use with preservation of bone mineral density of the lumbar spine in postmenopausal women.[39] In another trial, the risk of fatal myocardial infarction was significantly decreased in patients receiving adjuvant tamoxifen for five years versus surgery alone.[37] Ophthalmologic toxicities have been reported in patients receiving tamoxifen; patients receiving tamoxifen who complain of visual problems should be assessed carefully.[40] The usual tamoxifen dose schedule is 10 mg taken twice daily. Recent evidence suggests that 20 mg taken once daily is bioequivalent.[41]

If ER status is used to select adjuvant treatment, the study should be performed in a well-established, skilled laboratory, and ER-indeterminate patients (either because of inadequate tissue sample or equivocal results) should be considered separately.

Proposals to treat elderly patients with tamoxifen alone with no surgery or

radiotherapy have been made. This approach has unacceptably high local recurrence rates and should be reserved for those patients who are not candidates for mastectomy or lumpectomy plus radiotherapy or who refuse these options. [42-45]

Treatment options:

Standard:

-- Initial surgical management --

The surgical procedure used for initial treatment depends on the location and size of the lesion, appearance of the mammogram, breast size, and how the patient feels about preservation of the breast. The primary advantage of lumpectomy plus radiotherapy (CS plus RT) is cosmesis with breast preservation. Long-term studies now indicate that survival is equivalent with either modified radical mastectomy or CS plus RT. [3,46] One of the major randomized trials comparing mastectomy to CS plus RT included data from an institution where falsified data have been documented. [3] Preliminary reanalysis of the study excluding all cases from this institution has been performed by the NSABP and the National Cancer Institute and there is no change in the conclusion from the trial, that CS plus RT is equivalent to mastectomy in overall survival. The preliminary reanalysis is available on CancerFax, CancerNet, and in PDQ News. A complete, formal analysis is underway and will be published as soon as possible. Infiltrating ductal, lobular, medullary, colloid, and tubular invasive breast cancer can all be well-treated with CS plus RT. [47] Because local recurrence in the breast occurs in as many as 20% of patients choosing CS plus RT, patients should be monitored carefully for this occurrence. Subsequent mastectomy will control the disease in most of these patients. [46] The incidence of locally recurrent disease in the ipsilateral breast seems to be higher in patients under 35 years of age; these patients should be watched carefully. [48] If CS plus RT is elected for any age group, the primary tumor should be completely excised. There is a debate as to whether completely clear microscopic margins are necessary. [49] A group from the Joint Center for Radiation Therapy (JCRT) and others have used extensive intraductal component (EIC) as a histopathologic marker to determine extent of resection. [50-54] If EIC is prominently present within the tumor or is present in grossly normal adjacent breast tissue, a more extensive resection to remove residual intraductal carcinoma is performed. If this would leave a cosmetically unacceptable result, a mastectomy is done.

Radiotherapy consists of external-beam irradiation plus a boost to the primary tumor site. The boost can be given with either an interstitial radioactive implant or external irradiation, generally with electrons. Absolute need for the boost has not yet been proven. [3] Radiotherapy must be used to treat the remaining breast tissue, since at least 40% of women undergoing lumpectomy alone without irradiation will experience recurrence within the ipsilateral breast. [4] Nodal irradiation may not be required in patients who have had axillary dissections, since regional nodal failure is uncommon when the breast alone is irradiated. [55]

Surgical and radiotherapeutic techniques are extremely important in obtaining an optimal therapeutic result and satisfactory cosmesis. The availability of specialized equipment and radiation oncologists with expertise using this equipment should be considered in the selection of treatment. Radiation side effects that can be minimized with careful attention to technique include: myocardial damage for left-sided breast lesions, radiation pneumonitis, arm edema, brachial plexopathy, and the risk of second malignancies. Long-term cardiovascular mortality has been reported in patients receiving postmastectomy radiotherapy with deep tangential cobalt-60 fields for

left-sided tumors.[56] Sarcomas in the treatment port and secondary leukemias are very rare. One report suggests an increase in contralateral breast cancer for women under age 45 who have received chest wall irradiation after mastectomy.[57] There is no increased risk of contralateral breast cancer for women given radiotherapy after age 45.[58] Modern techniques to minimize the radiation dose to the contralateral breast should be used to keep the absolute risk as low as possible.[59]

Women who opt for radiotherapy should be followed carefully with regular mammography and physical examination to detect asynchronous disease in remaining breast tissue in the ipsilateral breast.[60] Women treated with radiotherapy or mastectomy should also have regular physical and mammographic examinations of the contralateral breast because of the risk of a second primary.

The surgical procedures include:

1. Lumpectomy/segmental mastectomy/conservative surgery with separate axillary node dissection and radiotherapy to the breast.[3,5,6,61]
2. Modified radical or total mastectomy with axillary dissection.[62,63]

-- Adjuvant therapy --

1. For suitable ER-negative patients, adjuvant chemotherapy with a proven effective regimen.[18,20] There is continuing controversy concerning the routine use of adjuvant chemotherapy in all patients with ER-negative, node-negative cancers. Patients with a poor prognosis (manifested by poor nuclear differentiation, tumor necrosis, and tumor size greater than 2.0 cm) are reasonable candidates for adjuvant chemotherapy. A number of studies have been reported recently, however, that indicate that a group of patients with small tumors who probably would not benefit from adjuvant chemotherapy could be identified. These include patients with more favorable histologic types of breast cancer, with tumors less than 1.0 cm in size, and with diploid tumors with less than a 10% fraction of cells in S phase.[1]
2. For ER-positive patients, adjuvant tamoxifen with an established schedule.[21]

In completed trials, adjuvant therapy was initiated within 6 weeks of surgery. Whether adjuvant therapy is effective if initiated at a later time is unknown.

Under clinical evaluation:

1. Other adjuvant chemotherapy or hormonal therapy.
2. No adjuvant therapy for selected subsets of patients with favorable prognostic factors.

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DIAGNOSIS #1 OF 1

03/19/96 15:5

FREQUENT CHANGES EXPECTED

-----BREAST CANCER-----

PROGNOSIS

(Separate statements containing information on prevention of breast cancer, screening for breast cancer, and breast cancer and pregnancy are also available in PDQ.)

Breast cancer, which is highly treatable by surgery, radiotherapy, chemotherapy, and hormonal therapy, is most often curable when detected in early stages. Mammography is the most important screening modality for the early detection of breast cancer. Breast magnetic resonance imaging is under study as a diagnostic tool.[1] Prognosis and selection of therapy are influenced by the age of the patient,[2] stage of the disease, pathologic characteristics of the primary tumor including the presence of tumor necrosis,[3] estrogen-receptor (ER) and progesterone-receptor (PR) levels in the tumor tissue, and measures of proliferative capacity, as well as by menopausal status and general health. Since criteria of menopausal status vary widely, age greater than 50 can be substituted as a definition of the postmenopausal state. Overweight patients may have a poorer prognosis.[4] Prognosis may also vary by race, with blacks, and to a lesser extent Hispanics, having a poorer prognosis than whites.[5] Breast cancer is classified into a variety of cell types, but only a few of these affect prognosis or selection of therapy. Rarely, the breast may be involved by other tumors such as melanoma, lymphoma, or sarcoma.

Female relatives of patients with breast cancer may face an increased risk of the disease. Age-specific risk estimates are currently available to help counsel these women and to design screening strategies for them.[6,7] It is estimated that approximately 5% of all women with breast cancer may have the recently identified germ-line mutation(s) in a gene (BRCA1) localized to chromosome 17q21. Their relatives, if carriers of the BRCA1 mutation(s), may face an 85% lifetime risk of breast cancer with 50% of the breast cancers occurring prior to age 50. Ovarian cancer risk may also be elevated.[8] A second gene, BRCA2, has also been localized to chromosome 13q12-13 but its exact sequence and location has not yet been identified. BRCA2 confers a high risk of breast cancer but not of ovarian cancer.[9] As practical assays are developed and validated, such detectable genetic abnormalities may be used to screen members of high-risk families.[10-12]

Patient management following initial diagnosis of breast cancer generally includes confirmation of the diagnosis, evaluation of stage of disease, and selection of therapy. Diagnosis may be confirmed by aspiration cytology, core needle biopsy, or incisional or excisional biopsy. At the time the tumor tissue is surgically removed, part of it should be processed for determination of ER and PR levels. Assay procedures are technically demanding, and the laboratory should use appropriate quality control procedures.[13] Charcoal, enzyme immunoassay, or enzyme immunocytochemical assays may be done.[14-16]

Although anatomic stage (size of primary tumor, axillary node status) remains an important prognostic factor,[17-20] other histologic and biologic characteristics may have predictive value.[21,22] Studies from the National Surgical Adjuvant Breast and Bowel Project (NSABP) [13] and the International Breast Cancer Study Group (IBCSG) [23] have shown that tumor nuclear grade and histologic grade, respectively, are significant indicators of outcome following adjuvant therapy for breast cancer. Morphologically determined tumor necrosis may be a prognostic variable for early recurrence.[3] However, the prognostic significance of these pathologic factors outside these study groups is unclear. In addition, the IBCSG has reported that serial sectioning of ipsilateral axillary lymph nodes judged to be disease-free after routine histologic

examination reveals micrometastases in 9% of breast cancer patients and may identify a higher-risk "node-negative" population, [24] confirming reports by Friedman et al. [25] There is substantial evidence that ER status and measures of proliferative capacity of the primary tumor (thymidine labeling index or flow cytometric measurements of S-phase and ploidy) may have significant independent predictive value. [26-29] In stage II disease, the PR status may have greater prognostic value than the ER status. Tumor microvessel density, c-erbB-2, c-myc, p53 expression, and peritumoral lymphatic vessel invasion may also be prognostic indicators in patients with node-negative breast cancer. [30-35]

Several retrospective reviews demonstrate a significantly better disease-free survival for premenopausal women with breast cancer and positive axillary lymph nodes operated on during the luteal phase (days 15-36) as compared to those operated on during the follicular phase (days 0-14) of their menstrual cycle. [36-38] However, several other studies have failed to confirm this finding or have found opposite results. [39-41] Because of the inconsistent results of these studies, it would be premature to mandate a modification in the scheduling of breast cancer operations according to the patient's menstrual cycle.

Pathologically, breast cancer is frequently a multicentric disease. However, clinical diagnosis of two or more primary cancers in a single breast is uncommon. [42] Similarly, simultaneous bilateral breast cancer is unusual. It is more common in patients with infiltrating lobular carcinoma. Patients who have breast cancer should have bilateral mammography at the time of diagnosis to rule out synchronous disease. They should also continue to have regular breast physical examinations and mammography to detect either asynchronous disease in the ipsilateral breast in those patients treated with lumpectomy and radiotherapy or a second primary cancer in the contralateral breast. [43] The risk of a primary breast cancer in the contralateral breast is significant, approximately 1% per year. [22,44] Patient age of less than 55 years at the time of diagnosis or lobular tumor histology appear to increase this risk to 1.5%. [45] The development of a contralateral breast cancer is associated with an increased risk of recurrence. [46]

Some retrospective studies suggest that perioperative blood transfusion impairs survival in breast cancer patients. [47] Although other retrospective studies have not confirmed the association between transfusion and prognosis, [48] limiting the transfusion of blood to breast cancer patients whenever medically feasible seems prudent. A modified radical mastectomy rarely requires blood transfusion if performed by an experienced surgeon, even when combined with submuscular insertion of an implant to restore breast contour. When breast contour following modified radical mastectomy is to be restored using a tissue flap, the need for blood transfusions should be anticipated. Provision for autologous blood transfusions in that setting is strongly recommended.

Even when standard therapy is effective, patients with breast cancer are appropriately considered as candidates for clinical trials designed to improve therapeutic results and decrease the morbidity of treatment. There is convincing evidence from randomized trials that periodic screening with bone scans, liver sonography, chest x-rays, and blood tests of liver function do not improve survival or quality of life when compared to routine physical exams. [49,50] Even when these tests permit earlier detection of recurrent disease, patient survival is unaffected. [50] Based on these data, acceptable follow-up for asymptomatic patients after completion of their treatment for stages I-III breast cancer can be limited to physical examination along with annual mammography. The intensity of follow-up and the appropriateness of screening tests after the completion of primary treatment for stages I-III breast cancer remain controversial.

Increasingly, hormone replacement therapy (HRT) is prescribed for many postmenopausal women in the U.S. both to decrease acute menopausal symptoms and to promote long term health benefits. More precise quantitation of those latter benefits with current HRT regimens is presently under study (Women's Health Initiative Trial), but the benefits are potentially important. With rising numbers of breast cancer survivors, many of whom are entering menopause prematurely due to adjuvant hormonal or chemotherapy treatment, HRT for these women poses a dilemma. HRT is generally not used for women with breast cancer because estrogen is a proven growth factor for most breast cancer cells in the laboratory. However, a review of the literature makes several pertinent observations based on clinical trials.[51] Postmenopausal women with no history of breast cancer who receive HRT do not appear to have an appreciably higher risk of the disease, although some studies have shown an increased risk with prolonged use (> 5 years) of HRT.[52] In addition, the prognosis of women who took HRT before developing breast cancer appears better than that of women with no such exposure. This may be a result of increased surveillance leading to detection of tumors at an earlier stage and may not be a result of the HRT.[53] Neither pregnancy after breast cancer nor the use of oral contraceptive pills before a diagnosis of breast cancer adversely impact survival when controlled for stage of disease. These findings provide the rationale for prospective clinical trials testing the impact of HRT on breast cancer recurrence and on the development of new tumors. Such research is planned in carefully selected women with breast cancer at relatively low risk of relapse. The routine use of HRT should await these results.

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CELLULAR CLASSIFICATION

Infiltrating or invasive ductal cancer is the most common cell type, comprising 70%-80% of all cases.

Lobular carcinoma involves both breasts more frequently than other histologic types.

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass.[1] Radiologically there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumor embolization of dermal lymphatics. Inflammatory carcinoma is classified as T4d.

The following is a list of breast cancer histologic classifications:[1]

ductal

- intraductal (in situ)
- invasive with predominant intraductal component
- invasive, NOS (not otherwise specified)
- comedo
- inflammatory
- medullary with lymphocytic infiltrate
- mucinous (colloid)
- papillary
- scirrhous
- tubular
- other

lobular

- in situ
- invasive with predominant in situ component
- invasive

nipple

- Paget's disease, NOS
- Paget's disease with intraductal carcinoma
- Paget's disease with invasive ductal carcinoma

undifferentiated carcinoma

The following are tumor subtypes that occur in the breast, but are not considered to be typical breast cancers:

cystosarcoma phyllodes

Cystosarcoma phyllodes is a rare variant of breast cancer generally treated with wide local excision. Although most patients are cured with such treatment, the risk of developing local recurrence or metastases is related to infiltrating margins, degree of stromal mitotic activity, nuclear pleomorphism, and stromal overgrowth. [2,3]

angiosarcoma

primary lymphoma

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STAGE INFORMATION

This staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions are formulated in part according to staging categories but primarily according to lymph node status, ER and PR receptor levels in the tumor tissue, menopausal status, and the general health of the patient.

Stages are defined by TNM classification. [1]

-- TNM definitions --

Primary tumor (T):

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated tumor mass*

T1: Tumor 2.0 cm or less in greatest dimension**

T1a: 0.5 cm or less in greatest dimension

T1b: More than 0.5 cm but not more than 1.0 cm in greatest dimension

T1c: More than 1.0 cm but not more than 2.0 cm in greatest dimension

T2: Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension**

T3: Tumor more than 5.0 cm in greatest dimension**

T4: Tumor of any size with direct extension to chest wall or skin

Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

T4a: Extension to chest wall

T4b: Edema (including peau d'orange), ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c: Both of the above (T4a and T4b)

T4d: Inflammatory carcinoma

*Note: Paget's disease associated with tumor mass is classified according to the size of the tumor.

**Note: Dimpling of the skin, nipple retraction, or other skin changes may occur in T1, T2, or T3 without changing the classification.

Regional lymph nodes (N):

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)

N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral axillary lymph node(s)

N2: Metastasis to ipsilateral lymph node(s) fixed to one another or to other structures

N3: Metastasis to ipsilateral internal mammary lymph node(s)

Pathologic classification (pN):

pNX: Regional lymph nodes cannot be assessed (not removed for study or previously removed)

pN0: No regional lymph node metastasis

pN1: Metastasis to movable ipsilateral axillary node(s)

pN1a: Only micrometastasis (none larger than 0.2 cm)

pN1b: Metastasis to lymph node(s), any larger than 0.2 cm

pN1bi: Metastasis in 1 to 3 lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension

pN1bii: Metastases to 4 or more lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension

pN1biii: Extension of tumor beyond the capsule of a lymph node metastasis less than 2.0 cm in greatest dimension

pN1biv: Metastasis to a lymph node 2.0 cm or more in greatest dimension

pN2: Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures

pN3: Metastasis to ipsilateral internal mammary lymph node(s)

Distant metastasis (M):

MX: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)

-- Stage 0 --

Stage 0 (in situ) breast cancer is defined by the following TNM group:

Tis, N0, M0

-- Stage I --

Stage I breast cancer is defined by the following TNM group:

T1, N0, M0

-- Stage II --

Stage IIA breast cancer is defined by the following TNM groups:

T0, N1, M0

T1, N1,* M0

T2, N0, M0

*The prognosis of patients with N1a disease is similar to that of patients with pN0 disease.

Stage IIB breast cancer is defined by the following TNM group:

T2, N1, M0

T3, N0, M0

-- Stage III --

Stage IIIA breast cancer is defined by the following TNM groups:

T0, N2, M0

T1, N2, M0

T2, N2, M0

T3, N1, M0

T3, N2, M0

Stage IIIB breast cancer is defined by the following TNM groups:

T4, any N, M0
any T, N3, M0

-- Stage IV --

Stage IV breast cancer is defined by the following TNM group:

any T, any N, M1

-- Inflammatory breast cancer --

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiologically there may be a detectable mass and characteristic thickening of the skin over the breast. The clinical presentation is due to tumor embolization of dermal lymphatics or to capillary congestion. Inflammatory carcinoma is classified T4d.

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TREATMENT OVERVIEW

The choice of state-of-the-art treatment for breast cancer is influenced by tumor stage and ER and PR levels and by patient age and menopausal status. All newly diagnosed patients with breast cancer may appropriately be considered as candidates for one of the numerous ongoing clinical trials designed to improve survival and decrease the morbidity of current conventional treatment.

Reconstructive surgery:

For breast cancer in situ and stage I and II infiltrating cancer, reconstructive surgery may be employed if a mastectomy is performed. It may be done at the time of the mastectomy (immediate reconstruction) or at some subsequent time (delayed reconstruction) in an attempt to restore the anatomical deficit of the mastectomy.[1-4] Breast contour can be restored either by the submuscular insertion of an artificial implant (silicone or saline-filled) or by a rectus muscle or other flap. Both procedures offer satisfactory cosmetic results. Insertion of an artificial implant is a relatively simple procedure. A saline-filled tissue expander can be inserted beneath the pectoral muscle. Saline is used to expand it over a period of weeks or months until the desired volume is obtained. The tissue expander is then replaced by a permanent implant. Rectus muscle flaps, which offer a better cosmetic result, require a considerably more complicated and prolonged operative procedure, and blood transfusions may be required. There is no convincing evidence that a silicone implant induces cancer or autoimmune disease. Problems associated with silicone implants include contracture of the capsule around the implant causing hardening and pain, rupture of the implant with release of the silicone gel, and infection.[5-7] In rare instances, either procedure could make a local recurrence more difficult to detect. Following breast reconstruction, radiotherapy can be delivered to the chest wall and regional nodes either in the adjuvant setting or upon local disease recurrence. Although this does not adversely affect outcome, cosmesis may be affected and the incidence of capsular fibrosis, pain, or the need for implant removal may be increased.[6] The use of silicone implants for breast augmentation may make the early detection of breast cancer more difficult by obscuring and compressing breast parenchyma.[5,7-9] The FDA has announced that silicone breast implants will be available only through controlled clinical studies. Women who wish to undergo reconstructive surgery following mastectomy will be assured access to those studies. However, the FDA has placed no restrictions on the use of saline-filled breast implants, which may constitute a reasonable alternative.

A separate statement containing information on breast cancer and pregnancy is also available in PDQ.

The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.

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TREATMENT BY STAGE/CELL TYPE BREAST CANCER IN SITU

Carcinoma in situ is classified as either intraductal carcinoma in situ (DCIS) arising from ductal epithelium or lobular carcinoma in situ (LCIS) arising from the epithelium of the lobules.[1] With the increasing use of screening mammography, noninvasive cancers are more frequently diagnosed and now constitute 15%-20% of all breast cancers. DCIS usually presents as microcalcifications or as a soft-tissue abnormality. There are several histologic subtypes: micropapillary, papillary, solid, cribriform, and comedocarcinoma. Some evidence suggests that comedocarcinoma may be more aggressive and associated with a higher probability of microinvasion.[2] LCIS is usually an incidental finding when a biopsy is done for some other abnormality. It is considered a marker for the subsequent development of invasive disease rather than a premalignant lesion. Because it may be difficult to distinguish DCIS from atypical hyperplasia and because certain forms of DCIS may be confused with LCIS, it may be helpful to obtain a second histopathologic interpretation of the biopsy specimen.

-- Intraductal carcinoma --

The customary treatment for DCIS has been mastectomy. This treatment results in a combined local and distant recurrence rate of 1%-2%. Experience with conservative surgery and radiotherapy suggests that it is a reasonable alternative. Breast cancer recurrence rates of 9%-21% are seen, and one-half of these recurrences are invasive carcinomas. Salvage of recurrences with mastectomy is feasible, and survival remains excellent and comparable to primary mastectomy.[3] Although no randomized comparisons of mastectomy versus conservative surgery plus breast irradiation have been done, the NSABP B-17 trial randomly assigned 790 women with localized DCIS and negative margins following excisional biopsy to breast irradiation (50 Gy) or no further

therapy.[4] On both treatment arms, 80% of the patients were diagnosed by mammography and 70% had small lesions (≤ 1.0 cm). In the irradiation group, 5-year event-free survival was improved, due entirely to a decrease in ipsilateral breast cancers. At 5 years, the cumulative incidence of recurrent DCIS was reduced by irradiation from 10.4% to 7.5% ($p = 0.05$), and, more importantly, occurrence of invasive cancer decreased from 10.5% to 2.9% ($p < 0.001$). Overall, only 3 deaths (0.4%) from breast cancer have been reported thus far in this trial, which is not appreciably different from the mortality reported in mastectomy series. The NSABP investigators concluded that local excision and breast irradiation is an acceptable alternative to mastectomy for treatment of localized DCIS.

To determine whether patients at high risk for recurrence could be identified, the NSABP analyzed the pathologic material submitted for central review from 573 of the original cohort of 790 women randomized in B-17.[5] Only the absence of clear tumor margins and moderate to marked comedonecrosis were independent predictors of ipsilateral breast tumor recurrence. However, even among cases with these risk factors, the rate of recurrence after local excision and irradiation was not sufficiently increased to make mastectomy necessarily preferable to local excision and irradiation.

In addition to the B-17 randomized study results, several retrospective, nonrandomized series from single institutions have demonstrated that there is a low ipsilateral recurrence rate following local excision alone. Recurrence and the occurrence of invasive cancer appear to decrease with the addition of breast irradiation, even for the lowest risk lesions, and this knowledge should be factored into the decision-making process of those choosing excision alone. There is currently much debate among pathologists over how to best identify low-risk DCIS lesions. Several pathologic staging systems have been developed and tested retrospectively, but consensus recommendations have not been achieved.[6-9]

Patients with nonpalpable lesions and microcalcifications detected on mammography who are considered for breast-conserving treatment should undergo careful mammographic evaluation prior to biopsy, followed by needle localization biopsy. Specimen radiography should be performed to confirm that the lesion has been excised and to direct pathologic sampling. A pathologist should give a careful gross description of the excised specimen and should ink the specimen margins before sectioning to facilitate margin evaluation on permanent section. The relation between the calcifications and the lesion and the distance from the tumor to the inked margins of resection should be described. Following biopsy, mammography should be repeated to confirm that all suspicious microcalcifications have been removed. If residual microcalcifications are seen on post-biopsy mammography, the primary site should be re-excised prior to beginning radiotherapy. The choice of treatment when there is margin involvement by tumor is a controversial issue. Frequently, if the original excision reveals positive margins, a re-excision is done. Then, the extent of disease in the re-excision is evaluated and a decision is made as to whether radiotherapy or mastectomy is appropriate. A simultaneous low axillary dissection is not mandatory as positive lymph nodes are rare.[10] Those patients in whom lymph node involvement is documented should be managed as described under stage II.

Surgical and radiotherapeutic techniques are extremely important in obtaining an optimal therapeutic result and satisfactory cosmesis. The availability of specialized equipment and radiation oncologists with expertise using these techniques should be considered in the selection of treatment. Radiation side effects that can be minimized with careful attention to technique include: myocardial damage for left-sided breast lesions, radiation pneumonitis, arm edema, brachial plexopathy, and the risk of second malignancies. Sarcomas in

the treatment port and secondary leukemias are very rare. One report suggests an increase in contralateral breast cancer for women under the age of 45 who have received radiation. Modern techniques to minimize radiation dose to the contralateral breast should be used to keep the absolute risk as low as possible. [11,12] Patients with persistent microscopic involvement of margins after local excision or with a diagnosis of DCIS and evidence of suspicious, diffuse microcalcifications have usually been treated with mastectomy. The NSABP has recently completed accrual to a trial (B-24) comparing two different treatment options for these patients. In this trial, 1,800 women with such lesions were randomly assigned, following local excision, to receive either irradiation plus tamoxifen or irradiation plus placebo, but the results are not yet available. As a consequence, tamoxifen should not be used for DCIS outside of a clinical trial.

Women who opt for radiotherapy for DCIS should be followed carefully with regular mammography and physical examination to detect asynchronous disease in breast tissue remaining in the ipsilateral breast. [13] Women treated with radiotherapy or mastectomy should also have regular physical and mammographic examinations of the contralateral breast because of the risk of a second primary.

-- Lobular carcinoma in situ --

LCIS is a controversial term; some prefer to call this lesion "lobular neoplasia." The lesion is generally widely distributed throughout the breast and is frequently bilateral. It is considered a marker for the subsequent development of invasive disease rather than a pre-malignant lesion. The patient with LCIS has a 25% chance of developing an invasive cancer (either lobular or, more commonly, infiltrating duct cancer) in either breast within 25 years. The incidence of subsequent cancer is not related to the extent of focal areas of LCIS within the breast. The clinical management of the patient with LCIS is controversial; options include no treatment after biopsy with careful follow-up (physical examination and mammography) or bilateral prophylactic mastectomies. Axillary lymph node dissection is not necessary for the in situ lesion. Many physicians favor periodic examination and mammography without therapy, provided the patient is aware of the risk of developing invasive cancer and is also aware of the possibility of developing metastatic cancer before a clinical diagnosis is established. [14,15] Patients who have undergone local excision for LCIS are eligible for a large multicenter clinical trial of tamoxifen to prevent development of invasive cancer. [16]

Treatment options for intraductal carcinoma (DCIS): [17-22]

Standard:

1. Total mastectomy.
2. Lumpectomy with radiotherapy.

Under clinical evaluation:

Lumpectomy alone or with tamoxifen.

Treatment options for lobular carcinoma in situ (LCIS): [23-25]

Standard:

1. Long-term periodic examination with yearly mammography and follow-up after biopsy without further therapy.
2. Bilateral total mastectomy with or without low axillary dissection.

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TREATMENT BY STAGE/CELL TYPE STAGE I BREAST CANCER

Stage I breast cancer is often curable with a variety of surgical procedures. However, 10-20 year follow-up of patients managed with surgery alone now reveals that as many as 21% may ultimately relapse.[1] Surgical procedures that conserve a major portion of the involved breast, followed by radiotherapy, provides tumor control equivalent to more extensive surgical procedures. The diagnostic biopsy and the surgical procedure that will be used as initial treatment are often performed as two separate procedures. After the presence of a malignancy is confirmed and the histology is determined, treatment options should be discussed with the patient before definitive therapy is recommended. ER and PR status should be determined for the primary tumor.[2]

In many cases, the diagnosis of breast carcinoma using fine needle aspiration cytology may be sufficient to confirm malignancy. It is then appropriate to discuss the therapeutic options to help the patient with the treatment decision. The surgeon may then proceed with a single, sequential procedure that includes biopsy, frozen section confirmation of carcinoma, and the surgery elected by the patient.

Surgical options include mastectomy, mastectomy with reconstruction, or conservative surgery plus radiotherapy (CS plus RT). Survival is equivalent with any of these options as documented in six prospective randomized trials.[3-8] Selection of the appropriate therapeutic approach depends on the location and size of the lesion, breast size, appearance of the mammogram, and how the patient feels about preservation of the breast. An axillary lymph node dissection should be performed for histologic study since approximately one-third of patients with clinically negative nodes will have histologic involvement and would be candidates for additional treatment as per stage II with positive axillary nodes. Although most authorities agree that an axillary node dissection in the presence of clinically negative nodes is a necessary staging procedure, controversy exists as to the extent of the procedure because of long-term morbidity (arm discomfort and swelling) associated with an axillary node dissection. Whether entire areas of potentially lymph-node-bearing tissue should be removed or whether staging can be accomplished by excision of a specific number of nodes is questioned. Evidence indicates that removal of five to ten nodes is a satisfactory staging procedure in patients with stage I disease.[9] Data also suggest that the level of lymph node involvement (I vs II vs III) does not add independent prognostic information to the total number of positive axillary nodes.[10] In addition, ER status, tumor size, and measures of proliferative capacity (thymidine labeling index, flow cytometry for measurement of S-phase and ploidy) are highly predictive for risk of relapse in the node-negative patient.[1,11,12] Some patients with stage I tumors appear to be at low risk of relapse (for

example, those with tumor size less than 1.0 cm or with more favorable histologic tumor types, e.g., medullary, mucinous, papillary, tubular) and may not require postoperative adjuvant hormonal therapy or chemotherapy.[13-15] High histologic grade of tumor and high rate of mitosis may identify a high-risk subset of patients with T1 lesions less than 1.0 cm.[16] A review of 20 years' experience illustrates the prognostic significance of tumor size and histologic grade in stage I tumors.[17]

-- Adjuvant therapy --

Because a significant number of patients with node-negative breast cancer ultimately have disease recurrence, several prospective randomized trials have studied adjuvant chemotherapy or hormonal therapy in node-negative breast cancer. Early trials using tamoxifen, including the Nolvadex Adjuvant Trial Organization (NATO) trial [18] and the Scottish trial, [19] suggested disease-free and overall survival benefit for node-negative patients but data were inconclusive. A small randomized trial comparing adjuvant chemotherapy with CMF versus no adjuvant therapy demonstrated improved disease-free and overall survival for poor-prognosis node-negative patients treated with CMF.[20,21]

Two large trials by the NSABP have demonstrated significant improvement in disease-free survival after five years of follow-up for ER-negative patients treated with adjuvant chemotherapy (methotrexate, fluorouracil, and leucovorin) [22] and for ER-positive patients treated with adjuvant tamoxifen.[23] Both of these large randomized trials demonstrate an early significant benefit for adjuvant therapy in these groups of node-negative breast cancer patients. In both studies, pre- and postmenopausal patients benefitted. An improvement in overall survival has been demonstrated at five years in postmenopausal ER-negative women treated with chemotherapy.[24] These trials, coupled with the three earlier trials and another intergroup adjuvant chemotherapy trial (INT-0011), demonstrated the efficacy of adjuvant treatment. At least five to ten years of further follow-up will be necessary to make a complete assessment of the impact of these therapies.[25-27]

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a meta-analysis of systemic treatment for early breast cancer by hormonal, cytotoxic, or biologic therapy methods in randomized trials involving 75,000 women with stage I or II carcinoma who were pre- or postmenopausal. In stage I and II postmenopausal women who were ER-positive, tamoxifen at 20 mg daily for at least 2 years (or perhaps longer) was found to prevent recurrent disease and increase survival, with the benefits of initial treatment persisting up to 10 years. Some evidence indicates that ER-negative women could receive similar benefits with tamoxifen treatment. There is a decreased incidence of carcinoma in the contralateral breast and decreased cardiovascular mortality in women treated with tamoxifen. Cytotoxic chemotherapy in the EBCTCG, usually with CMF for 6-12 months, was shown to decrease recurrences and increase survival in both pre- and postmenopausal women with stages I and II disease. The role of ovarian ablation in women under the age of 50 was also analyzed. It was found to produce a survival benefit comparable to that seen with chemotherapy in premenopausal women. This has raised the question again of whether a portion of the impact of systemic chemotherapy is through an endocrine mechanism - ovarian ablation. Such a mechanism of action has been postulated in other trials. In one study, a 12-week chemotherapy regimen induced menopause less frequently than a 36-week regimen and was associated with poorer survival.[28] An additional data-derived analysis of ovarian ablation and chemotherapy postulated an additive effect. The EBCTCG by an indirect analysis also postulated that there would be an additive effect of tamoxifen and cytotoxic chemotherapy in postmenopausal women.[29,30]

The use of adjuvant tamoxifen has been associated with certain toxic effects.

The most significant is the development of endometrial cancer which, in large clinical trials, has been reported to occur at a rate that is 2-7 times greater than that observed in untreated women.[31-34] A population-based observational study of women with breast cancer who took tamoxifen as adjuvant therapy for 2 years showed no increased risk of ovarian or endometrial cancer and a significant decrease in the risk of developing contralateral breast cancer.[35] There has been some concern raised about increased risk of gastrointestinal malignancy, but these findings are tentative and further study is needed.[36]

Patients on tamoxifen should be followed with annual pelvic exams and have timely evaluation of all extramenstrual uterine bleeding. Although one retrospective study raised concern that endometrial cancers in women on tamoxifen (40 mg/day) had a worse outcome and were characterized by higher grade lesions and a more advanced stage than in women not treated with tamoxifen, other larger studies using standard tamoxifen doses (20 mg/day) have failed to demonstrate this finding.[31,37] Similar to estrogen, tamoxifen produces endometrial hyperplasia which can be a premalignant change. In a cohort of women without a history of breast cancer randomized to receive tamoxifen or placebo on the British Pilot Breast Cancer Prevention Trial, 16% of those on tamoxifen developed atypical hyperplasia at varying times from the start of treatment (range 3-75 months, median 24 months) while no cases occurred on the control arm.[38] The value of endometrial biopsy, hysteroscopy, and transvaginal ultrasound as screening tools is unclear.[39] Management algorithms for women on tamoxifen who develop endometrial changes are being researched, but at the present time, there is no standard approach. Addition of progesterone to tamoxifen has not yet been proven to reverse endometrial changes caused by tamoxifen nor have its effects on breast cancer been adequately studied. Screening and management of any detected endometrial abnormalities must therefore be individualized, taking into account the risks and benefits of tamoxifen treatment.

Other toxic effects noted with tamoxifen include thromboembolic phenomena, which occurred with an increased frequency of approximately 1% in women on the NSABP trial.[24] Clotting factor changes have been reported in controlled studies of prolonged tamoxifen use at standard doses; antithrombin III, fibrinogen, and platelet counts have been minimally reduced in patients receiving tamoxifen. The relationship of these counts to thromboembolic phenomena is not clear.[40] Patients should be watched for this complication. Short-term toxic effects of tamoxifen in postmenopausal women may include vasomotor symptoms and gynecologic symptoms (vaginal discharge or irritation).[41] Clonidine can ameliorate hot flashes in some patients.[42] Tamoxifen therapy may also be associated with certain beneficial estrogenic effects including decreased total and low-density lipoprotein levels.[43,44] A large controlled Swedish trial has shown a decreased incidence of cardiac disease in postmenopausal women taking tamoxifen. Results were better for women taking tamoxifen for 5 years than in those taking it for 2 years.[45] In another trial, the risk of fatal myocardial infarction was significantly decreased in patients receiving adjuvant tamoxifen for 5 years versus those treated with surgery alone.[44] Controlled studies have associated long-term tamoxifen use with preservation of bone mineral density of the lumbar spine in postmenopausal women.[46-48] Ophthalmologic toxic effects have been reported in patients receiving tamoxifen; such patients who complain of visual problems should be assessed carefully.[49] The usual tamoxifen dosage is 10 mg twice daily, but evidence suggests that 20 mg once daily is bioequivalent.[50]

If ER status is used to select adjuvant treatment, the study should be performed in a well-established, skilled laboratory, and ER-indeterminate patients (either because of inadequate tissue sample or equivocal results) should be considered separately.

Proposals to treat elderly patients with tamoxifen alone with no surgery or radiotherapy have been made. This approach has unacceptably high local recurrence rates and, outside of a clinical trial setting, should be used only in patients who are not candidates for mastectomy or lumpectomy plus radiotherapy or who refuse these options. [51-54] Studies are currently addressing whether conservative surgery and tamoxifen without breast irradiation is acceptable treatment for women with tumors ≤ 1 cm [55] or for older women (≥ 70 years old) with tumors under 4 cm. [56]

Treatment options:

Standard:

-- Initial surgical management --

The surgical procedure used for initial treatment depends on the location and size of the lesion, appearance of the mammogram, breast size, and how the patient feels about preservation of the breast. The primary advantage of lumpectomy plus radiotherapy (CS plus RT) is cosmesis with breast preservation. Long-term, prospective, randomized studies now indicate that survival is equivalent with either modified radical mastectomy or CS plus RT. [3-7, 57, 58] Infiltrating ductal, lobular, medullary, colloid, and tubular invasive breast cancer can all be well-treated with CS plus RT. [59] Because local recurrence in the breast occurs in as many as 20% of patients choosing CS plus RT, patients should be monitored carefully for this occurrence. Subsequent mastectomy will control the disease in most of these patients. [7] The incidence of locally recurrent disease in the ipsilateral breast seems to be higher in patients under 35 years of age; these patients should be watched carefully. [60] If CS plus RT is elected for any age group, the primary tumor should be completely excised. There is a debate as to whether completely clear microscopic margins are necessary. [58, 61, 62] A group from the Joint Center for Radiation Therapy (JCRT) and others have used extensive intraductal component (EIC) as a histopathologic marker to determine extent of resection. [63-67] If EIC is prominently present within the tumor or is present in grossly normal adjacent breast tissue, a more extensive resection to remove residual intraductal carcinoma is performed. If this would leave a cosmetically unacceptable result, a mastectomy is done.

Radiotherapy consists of external-beam irradiation plus a boost to the primary tumor site. The boost can be given with either an interstitial radioactive implant or external irradiation, generally with electrons. Absolute need for the boost has not yet been proven. [3] Radiotherapy should be used to treat the remaining breast tissue. The trial by Veronesi et al. [68] demonstrated a low in-breast recurrence rate (3.8%) in a subset of women over age 55 treated by quadrantectomy alone. This study has a follow-up of 39 months and the quadrantectomy is a more extensive surgical procedure than is usually performed in the United States. In addition, none of the other three trials was able to reproduce these results or determine a subset that did not benefit from radiotherapy. Wide excision (lumpectomy) alone has been compared to wide excision followed by radiotherapy in four prospective, randomized trials. [3, 68-70] All of the trials demonstrate a high in-breast recurrence rate overall with wide-excision alone. Nodal irradiation may not be required in patients who have had axillary dissections, since regional nodal failure is uncommon when the breast alone is irradiated. [71]

Surgical and radiotherapeutic techniques are extremely important in obtaining an optimal therapeutic result and satisfactory cosmesis. The availability of specialized equipment and radiation oncologists with expertise using this equipment should be considered in the selection of treatment. Radiation side effects that can be minimized with careful attention to technique include: myocardial damage for left-sided breast lesions, radiation pneumonitis, arm

edema, brachial plexopathy, and the risk of second malignancies. Long-term cardiovascular mortality has been reported in patients receiving postmastectomy radiotherapy with deep tangential cobalt-60 fields for left-sided tumors.[72] Sarcomas in the treatment port and secondary leukemias are very rare. One report suggests an increase in contralateral breast cancer for women under age 45 who have received chest wall irradiation after mastectomy.[73] There is no increased risk of contralateral breast cancer for women given radiotherapy after age 45.[74] Modern techniques to minimize the radiation dose to the contralateral breast should be used to keep the absolute risk as low as possible.[75] The risk of lung cancer as a result of radiation exposure during treatment for breast cancer is minimal when modern dosimetry techniques are used. Smokers, however, may have a slightly increased risk of lung cancer in the ipsilateral lung.[76]

Women who opt for radiotherapy should be followed carefully with regular mammography and physical examination to detect asynchronous disease in remaining breast tissue in the ipsilateral breast.[77] Women treated with radiotherapy or mastectomy should also have regular physical and mammographic examinations of the contralateral breast because of the risk of a second primary.

Women who have initially undergone radiation and who develop a contralateral breast primary may be treated with lumpectomy plus radiation for this second tumor with excellent cosmetic results. The development of a contralateral breast cancer is associated with an increased risk of recurrence.[78]

The surgical procedures include:

1. Lumpectomy/segmental mastectomy/conservative surgery with separate axillary node dissection and radiotherapy to the breast.[3,57,79,80]
2. Modified radical or total mastectomy with axillary dissection.[81,82]

-- Adjuvant therapy --

1. For suitable ER-negative patients, adjuvant chemotherapy with a proven effective regimen.[20,22] There is continuing controversy concerning the routine use of adjuvant chemotherapy in all patients with ER-negative, node-negative cancers. Patients with a poor prognosis (manifested by poor nuclear differentiation, tumor necrosis, and tumor size greater than 2.0 cm) are reasonable candidates for adjuvant chemotherapy. A number of studies have been reported recently, however, that indicate that a group of patients with small tumors who probably would not benefit from adjuvant chemotherapy could be identified. These include patients with more favorable histologic types of breast cancer, with tumors less than 1.0 cm in size, and with diploid tumors with less than a 10% fraction of cells in S phase.[1]
2. For ER-positive patients, adjuvant tamoxifen with an established schedule.[23]

In completed trials, adjuvant therapy was initiated within 6 weeks of surgery. Whether adjuvant therapy is effective if initiated at a later time is unknown.

Under clinical evaluation:

1. Studies of the value of more aggressive adjuvant chemotherapy for subsets of patients with unfavorable prognostic factors.[83,84]
2. No adjuvant therapy for selected subsets of patients with favorable prognostic factors.

3. Studies of the role of ovarian ablation for ER-positive patients. [85]

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TREATMENT BY STAGE/CELL TYPE STAGE II BREAST CANCER

Stage II breast cancer is curable with a range of accepted surgical procedures.

Surgical approaches that conserve a portion of the breast, followed by radiotherapy, can provide survival rates equivalent to more extensive surgery. The diagnostic biopsy and surgical procedure that will be used as primary treatment should be performed as two separate procedures. After the presence of a malignancy is confirmed and histology is determined, treatment options should be discussed with the patient before a definitive therapeutic procedure is recommended. ER and PR protein status should be determined for the primary tumor. [1]

In many cases, the diagnosis of breast carcinoma using fine needle aspiration cytology may be sufficient to confirm malignancy. It is then appropriate to discuss the therapeutic options to help the patient with the treatment decision. The surgeon may then proceed with a single, sequential procedure that includes biopsy, frozen section confirmation of carcinoma, and the surgery elected by the patient.

Surgical options include mastectomy, mastectomy with reconstruction, or conservative surgery (i.e., lumpectomy) plus radiotherapy (CS plus RT). Survival is equivalent with any of these options. [2-5] A complete, formal analysis is underway and will be published as soon as possible. Selection of one of the equivalent treatment options depends on the location and size of the lesion, analysis of the mammogram, breast size, and how the patient feels about preserving the breast. An axillary lymph node dissection should be done for staging purposes. In the situation of clinically positive nodes, the axillary dissection may have some local therapeutic benefit.

Postoperative chest wall radiotherapy after modified or total mastectomy should not be given routinely. It should be considered in selected patients who are known to have residual tumor in the operative field or may be in the high-risk group for locoregional failure, including those with four or more involved axillary nodes. Radiotherapy can decrease locoregional recurrence in this group even among those who receive adjuvant chemotherapy. [6-8] An update of a meta-analysis of randomized trials using radiotherapy after mastectomy reported a decrease in deaths due to breast cancer in patients who received radiotherapy. [9]

Proposals to treat elderly patients with tamoxifen alone with no surgery or radiotherapy have been made. This approach has unacceptably high local recurrence rates and, outside of a clinical trial setting, should be used only in patients who are not candidates for mastectomy or lumpectomy plus radiotherapy or who refuse these options. [10,11] A study is underway in which patients treated with lumpectomy plus tamoxifen are randomized to receive or not to receive radiotherapy. [12]

-- Stage II positive nodes --

Adjuvant combination chemotherapy has been found to prolong the disease-free interval and survival for pre- and postmenopausal patients with positive nodes. The standard duration of administration of such chemotherapy does not exceed one year. For node-positive postmenopausal women with hormone-receptor-positive tumors, adjuvant hormonal therapy with the relatively nontoxic antiestrogen tamoxifen prolongs disease-free interval and perhaps survival. In this setting, tamoxifen should be given for at least two years. CA and CMF seem to produce similar results in terms of disease-free survival in

both pre- and postmenopausal patients, but there are differences in toxicity that may influence the choice of regimen.[13] For some postmenopausal patients with negative hormone receptors, these small advantages may outweigh the toxicity of chemotherapy.[14] Long term follow-up of women who received cyclophosphamide-containing adjuvant chemotherapy for treatment of breast cancer indicates that the incidence of other solid tumors and secondary leukemia is not much higher than that in the general population.[15] In a trial by the NSABP (B-16), node-positive women 50-59 years of age who were PR+ and women 60 years of age and older irrespective of receptor status had improved disease-free and overall survival when treated with tamoxifen and chemotherapy (doxorubicin plus cyclophosphamide) compared to those treated with tamoxifen alone.[16] A report from the Eastern Cooperative Oncology Group (ECOG), comparing CMFP and CMFPT to surgery alone in node-positive postmenopausal patients, demonstrated disease-free survival benefit for CMFP chemotherapy in ER-negative patients, but overall survival was not prolonged. CMFPT, given for 1 year, failed to improve either disease-free or overall survival. ER-positive women experienced no benefit on either regimen.[17] A Southwest Oncology Group (SWOG) study of node-positive, postmenopausal, ER+ women compared tamoxifen alone to CMFVP and CMFVP + tamoxifen. CMFVP alone or in combination with tamoxifen was not superior to tamoxifen alone. In both the SWOG and ECOG studies, the small number of patients entered into these studies may have limited the ability to detect small but important differences. Another small study has indicated that disease-free survival may be increased with prolonged therapy with tamoxifen and one year of CMFVP chemotherapy.[18] One study addresses time to starting adjuvant chemotherapy in node-positive patients and shows no advantage in disease-free survival when chemotherapy is initiated earlier than 6 weeks postsurgery.[19] The 10-year survival rate for both pre- and postmenopausal women receiving either 6 or 12 cycles of CMF has been shown to be identical.[7]

-- Stage II negative nodes --

Patients with stage IIA, node-negative breast cancer (T2 N0 M0) generally have a lower risk of recurrence than node-positive patients. Relapse may be related to a number of factors, including tumor size. In an analysis of patients with T2 N0 M0 breast cancer, there was a 33% chance of recurrence at 20 years for patients with T = 2.1-3.0 cm compared to 44% for T = 3.1-5.0 cm.[20] Because a significant number of patients with node-negative breast cancer ultimately have disease recurrence, several prospective randomized trials have studied adjuvant chemotherapy or hormonal therapy in node-negative breast cancer. Early trials, including the Nolvadex Adjuvant Trial Organization (NATO) trial [14] and the Scottish trial,[21] suggested disease-free and overall survival benefit for node-negative patients but data were inconclusive. A small randomized trial comparing adjuvant chemotherapy with CMF versus no adjuvant therapy showed improved disease-free and overall survival for poor-prognosis node-negative patients treated with CMF.[14,21-23]

Two large trials by the NSABP have demonstrated significant improvement in disease-free survival after four years follow-up for ER-negative patients treated with chemotherapy (methotrexate, fluorouracil, and leucovorin)[24] and for ER-positive patients treated with tamoxifen.[25] Both of these large randomized trials demonstrate an early significant benefit for adjuvant therapy in these groups of node-negative breast cancer patients, although an improvement in overall survival has not yet been demonstrated. In both studies, pre- and postmenopausal patients benefitted. These trials, coupled with the three earlier trials and another intergroup adjuvant chemotherapy trial (INT-0011), demonstrated the efficacy of adjuvant treatment. At least 5-10 years of further follow-up is necessary to make a complete assessment of the impact of these therapies.[26-28]

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a

meta-analysis of systemic treatment for early breast cancer by hormonal, cytotoxic, or biologic therapy methods in randomized trials involving 75,000 women with stage I or II carcinoma who were pre- or postmenopausal. In stage I and II postmenopausal women who were ER-positive, tamoxifen at 20 mg daily for at least 2 years (or perhaps longer) was found to prevent recurrent disease and increase survival, with the benefits of initial treatment persisting up to 10 years. Some evidence indicates that ER-negative women could receive similar benefits with tamoxifen treatment. There is a decreased incidence of carcinoma in the contralateral breast and decreased cardiovascular mortality in women treated with tamoxifen. Cytotoxic chemotherapy in the EBCTCG, usually with CMF for 6-12 months, was shown to decrease recurrences and increase survival in both pre- and postmenopausal women with stages I and II disease. The role of ovarian ablation in women under the age of 50 was also analyzed. It was found to produce a survival benefit comparable to that seen with chemotherapy in premenopausal women. This has raised the question again of whether a portion of the impact of systemic chemotherapy is through an endocrine mechanism - ovarian ablation. Such a mechanism of action has been postulated in other trials. In one study, a 12-week chemotherapy regimen induced menopause less frequently than a 36-week regimen and was associated with poorer survival.[29] An additional data-derived analysis of ovarian ablation and chemotherapy postulated an additive effect.

In the only direct comparison of CMF versus ovarian ablation, disease-free and overall survival rates were identical in 332 premenopausal women with stage II disease.[30] It was also postulated that there would be an additive effect of tamoxifen and cytotoxic chemotherapy in postmenopausal women.[31,32] Clinical trials that address these issues are ongoing.

The use of adjuvant tamoxifen has been associated with certain toxic effects. The most significant is the development of endometrial cancer which, in large clinical trials, has been reported to occur at a rate that is 2-7 times greater than that observed in untreated women.[33-36] Because of this, patients on tamoxifen should be followed with annual pelvic exams and have timely evaluation of all extramenstrual uterine bleeding. Although one retrospective study raised concern that endometrial cancers in women on tamoxifen (40 mg/day) had a worse outcome and were characterized by higher grade lesions and a more advanced stage than in women not treated with tamoxifen, other larger studies using standard tamoxifen doses (20 mg/day) have failed to demonstrate this finding.[33,37]

Similar to estrogen, tamoxifen produces endometrial hyperplasia which can be a premalignant change. In a randomized cohort of patients on tamoxifen or placebo, recruited from the British Pilot Breast Cancer Prevention Trial, 16% of those on tamoxifen developed atypical hyperplasia at varying times from the start of treatment (range 3-75 months, median 24 months) while no cases occurred on the control arm.[38] The value of endometrial biopsy, hysteroscopy, and transvaginal ultrasound as screening tools is unclear.[39] Management algorithms for women on tamoxifen who develop endometrial changes are being researched, but at the present time, there is no standard approach. Addition of progesterone to tamoxifen has not yet been proven to reverse endometrial changes caused by tamoxifen nor have its effects on breast cancer been adequately studied. Screening and management of any detected endometrial abnormalities must therefore be individualized, taking into account the risks and benefits of tamoxifen treatment.

Other toxic effects noted with tamoxifen include thromboembolic phenomena, which occurred with an increased frequency of approximately 1% in women in the NSABP trial.[26] Clotting factor changes have been reported in controlled studies of prolonged tamoxifen use at standard doses; antithrombin III, fibrinogen, and platelet counts have been minimally reduced in patients

receiving tamoxifen. The relationship of these counts to thromboembolic phenomena is not clear.[40] Patients should be watched for this complication. Short-term toxic effects of tamoxifen in postmenopausal women may include vasomotor symptoms and gynecologic symptoms (vaginal discharge or irritation).[41] Clonidine can ameliorate hot flashes in some patients.[42] Tamoxifen therapy may also be associated with certain beneficial estrogenic effects, including decreased total and low-density lipoprotein levels.[43,44] A large controlled Swedish trial has shown a decreased incidence of cardiac disease in postmenopausal women taking tamoxifen. Results were better for women taking tamoxifen for 5 years than in those taking it for 2 years.[45] In another trial, the risk of fatal myocardial infarction was significantly decreased in patients receiving adjuvant tamoxifen for 5 years versus those treated with surgery alone.[44] Controlled studies have associated long-term tamoxifen use with preservation of bone mineral density of the lumbar spine in postmenopausal women.[46-48] Ophthalmologic toxic effects have been reported in patients receiving tamoxifen; such patients who complain of visual problems should be assessed carefully.[49] The usual tamoxifen dosage is 10 mg twice daily, but evidence suggests that 20 mg once daily is bioequivalent.[50]

If ER status is used to select adjuvant treatment, the study should be performed in a well-established, skilled laboratory, and ER-indeterminate patients (either because of inadequate tissue sample or equivocal results) should be considered separately.

Treatment options:

Standard:

-- Initial surgical management --

The surgical procedure used for initial treatment depends on the location and size of the lesion, analysis of the mammogram, breast size, and how the patient feels about preservation of the breast. The primary advantage of conservative surgery (i.e., lumpectomy) with radiotherapy (CS plus RT) is cosmesis with breast preservation. Long-term, prospective, randomized studies now indicate that survival is equivalent with either modified radical mastectomy or CS plus RT.[2,4,51-54] Infiltrating ductal, lobular, medullary, colloid, and tubular invasive breast cancer can all be well-treated with CS plus RT.[55] Because local recurrence in the breast occurs in as many as 20% of patients choosing CS plus RT, patients should be monitored carefully for this occurrence. Subsequent mastectomy will control the disease in most of these patients.[51] The incidence of locally recurrent disease in the ipsilateral breast seems to be higher in patients under 35 years of age; these patients should be watched carefully.[56] If CS plus RT is selected for any age group, the primary tumor should be completely excised. There is a debate as to whether completely clear microscopic margins are necessary.[57-59] A group from the Joint Center for Radiation Therapy (JCRT) and others have used extensive intraductal component (EIC) as a histopathologic marker to determine the extent of resection.[60-64] If EIC is prominently present within the tumor or present in grossly normal adjacent breast tissue, a more extensive resection to remove residual intraductal carcinoma is performed. If this would leave a cosmetically unacceptable result, a mastectomy is done.

Radiotherapy consists of external-beam irradiation plus a boost to the primary tumor site. The boost can be given with either an interstitial radioactive implant or external irradiation, generally with electrons. The absolute need for the boost has not yet been proven.[2] Radiotherapy must be used to treat the remaining breast tissue. Wide excision (lumpectomy) alone has been compared to wide excision followed by radiotherapy in four prospective, randomized trials.[2,3,65,66] All of the trials demonstrate a high in-breast recurrence rate overall with wide-excision alone. The trial by Veronesi et

al.[3] demonstrated a low in-breast recurrence rate (3.8%) in a subset of women over age 55 treated by quadrantectomy alone. This has only a short follow-up and the quadrantectomy is an extensive surgical procedure infrequently performed in the United States. In addition, none of the other three trials was able to reproduce these results or determine a subset that did not benefit from radiotherapy. Nodal irradiation may not be required in patients who have had axillary dissections and have three or fewer positive level I nodes, since regional nodal failure is uncommon when the breast alone is irradiated.[67]

Surgical and radiotherapeutic techniques are extremely important in obtaining an optimal therapeutic result and satisfactory cosmesis. The availability of specialized equipment and radiation oncologists with expertise using this equipment should be considered in the selection of treatment. Radiation side effects that can be minimized with careful attention to technique include: myocardial damage for left-sided breast lesions, radiation pneumonitis, arm edema, brachial plexopathy, and the risk of second malignancies. Long-term cardiovascular mortality has been reported in patients receiving postmastectomy radiotherapy with deep tangential cobalt-60 fields for left-sided tumors.[6] Sarcomas in the treatment port and secondary leukemias are very rare. One report suggests an increase in the incidence of contralateral breast cancer for women under the age of 45 who have received chest wall irradiation after mastectomy.[68] There is no increased risk of contralateral breast cancer for women given radiotherapy after age 45.[69] Modern techniques to minimize the radiation dose to the contralateral breast should be used to keep the absolute risk as low as possible.[70]

Women who opt for radiotherapy should be followed carefully with regular mammography and physical examination to detect asynchronous disease in remaining breast tissue in the ipsilateral breast.[71] Women treated with radiation or mastectomy should also have regular physical and mammographic examinations of the contralateral breast because of the risk of a second primary tumor. Women who have initially undergone radiation and who develop a contralateral breast primary may be treated with lumpectomy plus radiation for this second tumor with excellent cosmetic results and a low complication rate. The development of a contralateral breast cancer is associated with an increased risk of recurrence.[72]

The surgical procedures include:

1. Lumpectomy/segmental mastectomy/conservative surgery with separate axillary node dissection and radiotherapy to the breast.[2,4,5,71]
2. Modified radical or total mastectomy with axillary dissection.[4,73,74]
3. Radical mastectomy (in selected circumstances only, if needed to accomplish complete tumor resection).

Radiotherapy to the chest wall and regional nodes should be considered for patients at high risk of local-regional recurrence, including those with known residual disease or four or more involved nodes.

-- Adjuvant therapy --

1. Following the treatment used to control local disease, adjuvant combination chemotherapy is given to reduce the rate of recurrence and improve survival in pre- and postmenopausal node-positive patients. Many different drug regimens have been developed. Numerous studies have shown that combination chemotherapy is superior to single-agent treatment, and single-agent adjuvant chemotherapy should be avoided outside a clinical trial. The drug combinations listed have been tested and provide therapeutic benefit. Not all have been compared to an untreated control group in prospective randomized trials.[75]

CMF: cyclophosphamide + methotrexate + fluorouracil.[76,77]
CAF: cyclophosphamide + doxorubicin + fluorouracil.[78]
CA +/- tamoxifen: cyclophosphamide + doxorubicin +/-
tamoxifen.[13,16,79]
CMFVP: cyclophosphamide + methotrexate + fluorouracil + vincristine +
prednisone.[80]

Data from the NSABP-B-16 protocol indicate that hormonally responsive women over 50 years of age had a better disease-free survival following treatment with tamoxifen plus CA or tamoxifen plus PAF than with tamoxifen alone. No drug interaction was apparent between tamoxifen and the chemotherapy drugs.[16]

Dose intensity:

Recent retrospective analyses have indicated that the intensity of dose delivery may be important in the clinical outcome. The results of one study suggest that drug doses should not be reduced arbitrarily.[81] Dose intensity is expressed in mg/sqm/week. Analyses of trials using a combination of drugs have, in general, given equal weight to the "effective drugs" and have assigned a zero value if a given "standard drug" is not used in a particular regimen. Therefore, there is some degree of subjectivity to these analyses. Nevertheless, using such analyses, response rate (in advanced breast cancer) and freedom from relapse (in stage II breast cancer) have increased with increasing dose intensity. The steepest relationship between dose intensity and outcome has come from dose intensities of less than 0.8. Physicians should avoid arbitrary reductions in dose intensity.[82-84]

2. Following the treatment used to control local disease, adjuvant endocrine therapy with tamoxifen alone is given to reduce the rate of recurrence and probably improve survival in postmenopausal patients with lymph node involvement and positive hormone receptors. Tamoxifen, either alone or combined with chemotherapy, prolongs disease-free survival when administered for 24 months as adjuvant therapy to postmenopausal women with axillary lymph node metastases. It is probably of additional benefit when given for an even longer period of time.[14,21,23,85,86]

3. In node-negative patients:

For ER-negative patients or ER-positive patients with large tumors, adjuvant chemotherapy with a proven effective regimen.[22,24]
For ER-positive patients, adjuvant tamoxifen with an established schedule.[25]

In completed trials, adjuvant therapy was initiated within 6 weeks of surgery.

Whether adjuvant therapy is effective if initiated at a later time is presently unknown.

Under clinical evaluation:

1. Preliminary data indicate that primary (neoadjuvant) chemotherapy may allow breast conservation therapy in patients whose lesion and breast size would not otherwise have allowed this option.[87,88] Clinical studies are ongoing to further address this issue.
2. While significant advances have been made in the past 5 years, optimal adjuvant therapy continues to evolve for all subsets of patients. For this reason, all patients and their physicians are strongly encouraged to participate in controlled clinical trials.[89-92]
3. Clinical trials of high-dose chemotherapy with bone marrow transplantation in women with more than 10 positive lymph nodes and in those with 4-9 positive lymph nodes.[93,94]

4. Protocols evaluating new types of chemotherapy and/or hormone therapy.

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TREATMENT BY STAGE/CELL TYPE STAGE III BREAST CANCER

Stage III (locally advanced) breast cancer is further classified into stage IIIA and stage IIIB disease. Stage IIIA disease is often operable when

axillary lymph nodes are mobile. However, if the lymph nodes are fixed or if the tumor is very large, neoadjuvant chemotherapy is indicated to shrink the tumor before surgery.

-- Stage IIIA --

Treatment options:

Standard:

1. In operable cases, one of the following surgical procedures for initial treatment:
 - Modified radical mastectomy.
 - Radical mastectomy.
2. Because of the high risk of local recurrence for this stage, radiotherapy should be considered as part of the overall treatment plan:
 - Postoperative external-beam irradiation to the chest wall. A boost can be given if clinically indicated for positive or close margins.
3. Chemotherapy regimens with or without hormones are given in conjunction with the above surgical and radiotherapeutic procedures. Chemotherapy can be given prior to surgery in cases where primary resection is not feasible or is technically difficult. Some equally effective combination chemotherapy regimens commonly used are:
 - CMF: cyclophosphamide + methotrexate + fluorouracil.[1]
 - CAF: cyclophosphamide + doxorubicin + fluorouracil.[2,3]
 - CMFP: cyclophosphamide + methotrexate + fluorouracil + prednisone.[4]
 - CA: cyclophosphamide + doxorubicin.[5]
 - CMFVP: cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisone.[6]

Under clinical evaluation:

1. Clinical trials evaluating the role of combination chemotherapy with or without hormonal manipulation are ongoing.[7,8] Preliminary data indicate that neoadjuvant preoperative chemotherapy may allow breast conservation therapy in patients whose lesion and breast size would not have allowed this option.[9,10]
2. High-dose chemotherapy with hematopoietic stem cell support.

-- Stage IIIB (inoperable breast cancer, including inflammatory) --

The treatment of inflammatory breast cancer is similar to options for stage IIIB or IV breast cancer.[11]

In stage IIIB breast cancer, surgery is generally limited to the initial biopsy. Radiotherapy is used to treat locoregional disease and systemic chemotherapy is used to treat occult metastases. For patients with stage IIIB breast cancers, initial chemotherapy after biopsy and prior to local therapy with surgery or radiotherapy may result in tumor shrinkage and early systemic control. A recent preliminary report observed biopsy-confirmed complete responses of breast tumor masses following combination chemotherapy prior to local treatment. Surgical removal of residual tumor may be performed if a good response is achieved with the other therapies employed.

Treatment options:

Standard:

1. Incisional biopsy for diagnosis and receptor protein assay followed by preoperative chemotherapy. If the patient has a good response, local therapy with surgery and/or irradiation is recommended. If the response is poor, palliative radiotherapy with a cone-down field may be

recommended.

2. If combination chemotherapy is contraindicated, pretreatment with tamoxifen may be recommended for patients whose tumors are positive for ER and PR proteins.

Under clinical evaluation:

1. Phase II studies evaluating newly developed chemotherapeutic or biologic agents may be considered for patients whose local disease is not controllable by standard measures.
2. High-dose chemotherapy with hematopoietic stem cell support.

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TREATMENT BY STAGE/CELL TYPE STAGE IV BREAST CANCER

Stage IV breast cancer is often responsive to treatment with durable complete remissions attainable in 10%-20% of patients, although long disease-free

survival indicative of cure is rare.[1,2]

Surgical procedures are generally limited to those that will permit the determination of histology and ER and PR levels. Control of local disease is achieved with either surgery or radiotherapy. External-beam irradiation also has a major role in the palliation of symptoms, particularly pain caused by bone metastases. Appropriate patients should be considered for available trials studying the role of bisphosphonates in reducing skeletal morbidity in those with bony metastases. Preliminary results of a randomized trial of pamidronate in patients with bony metastatic disease show decreased skeletal morbidity in patients receiving this drug.[3] All patients with stage IV breast cancer should be considered candidates for one of the ongoing clinical trials in progress to improve therapeutic results in this disease.[4,5] For patients with recurrence after an anthracycline-containing regimen, paclitaxel (Taxol) has been approved by the Food and Drug Administration for second-line therapy.

Treatment options:

Standard:

1. A surgical biopsy to determine histology and ER and PR levels. External-beam radiotherapy or a hygienic mastectomy may be recommended to control local disease.
2. If visceral disease is absent and ER and PR status is positive, hormonal therapy is an excellent first treatment. One of the following equivalent approaches can be used:
 - Tamoxifen or oophorectomy for premenopausal patients.[6,7]
 - Antiestrogen therapy with tamoxifen for postmenopausal patients.
 - Progestational agents for postmenopausal patients.
3. If visceral disease is present or ER and PR status is negative, one of the following combination chemotherapy regimens will produce equivalent results:
 - CMF: cyclophosphamide + methotrexate + fluorouracil.[8]
 - CAF: cyclophosphamide + doxorubicin* + fluorouracil.[9]
 - CA: cyclophosphamide + doxorubicin.*[10]
 - CMFP: cyclophosphamide + methotrexate + fluorouracil + prednisone.[8]
 - CMFVP: cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisone.[9]

*The potential for doxorubicin-induced cardiotoxicity should be considered in the selection of chemotherapeutic regimens for an individual patient. Recognized risk factors for cardiac toxicity include advanced age, prior chest-wall irradiation, prior anthracycline exposure, hypertension, diabetes, and known underlying heart disease. The cardioprotective drug dexrazoxane (ICRF-187) has been shown in controlled studies to decrease the risk of doxorubicin-induced cardiac toxicity. The use of this agent has permitted patients to receive greater cumulative doses of doxorubicin and allowed patients with cardiac risk factors to receive doxorubicin.[11,12] The risks of cardiac toxicity may also be reduced by administering doxorubicin as a continuous intravenous infusion.[13]

Under clinical evaluation:

1. If visceral disease is absent and ER and PR status is positive, clinical trials evaluating the role of hormonal therapy should be considered as first treatment.[14]
2. If visceral disease is present or ER and PR status is negative, clinical trials evaluating the role of combination chemotherapy with and without

hormonal therapy should be considered as first treatment.

3. Phase II studies evaluating newly developed chemotherapeutic or biologic agents should also be considered. [15-18]
4. High-dose chemotherapy with hematopoietic stem cell support.

References:

1. Perry MC, Kardinal CG, Korzun AH, et al.: Chemohormonal therapy in advanced carcinoma of the breast: Cancer and Leukemia Group B protocol 8081. *Journal of Clinical Oncology* 5(10): 1534-1545, 1987.
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TREATMENT BY STAGE/CELL TYPE INFLAMMATORY BREAST CANCER

The treatment of inflammatory breast cancer is similar to options for stage IIIB or IV breast cancer.[1]

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TREATMENT BY STAGE/CELL TYPE RECURRENT BREAST CANCER

Recurrent breast cancer is often responsive to therapy although treatment is rarely curative at this stage of the disease. Radiotherapy has a major role in the palliation of locally recurrent disease and symptoms such as pain due to bone metastases. The ER and PR levels at the time of recurrence and previous treatment should be considered in selecting therapy. If ER and PR status is unknown or positive, then the site(s) of recurrence, disease-free interval, response to previous treatment, and menopausal status are useful in selecting chemotherapy or hormonal therapy.[1]

The results of one long-term trial indicate that between 10% and 20% of patients will have locally recurrent disease in the breast between 1 and 9 years after lumpectomy plus radiotherapy.[2] Local recurrence is usually the harbinger of widespread disease but, in a subset of patients, may be the only site of recurrence. For patients in this subset, surgery and/or radiotherapy may be curative.[3-5] Patients with chest wall recurrences of less than 3 cm, axillary and internal mammary node recurrence (not supraclavicular, which has a poorer survival), and a greater than 2-year disease-free interval prior to resection have the best chance for prolonged survival.[5] The 5-year disease-free survival rate (i.e., without further local or distant relapse) in one recent series of such patients was 25%, with a 10-year rate of 15%.[3] The locoregional control rate was 57% at 10 years.

The prognosis following breast cancer recurrence after lumpectomy plus radiotherapy is much better than that following chest-wall recurrence after mastectomy. Only 9%-25% of patients undergoing lumpectomy plus radiotherapy will be found to have distant metastases or locally extensive disease preventing mastectomy at the time of recurrence. In one series of 30 patients who failed locally after lumpectomy plus radiotherapy and who underwent salvage mastectomy, no distant recurrences were seen later than 6 years after initial local failure, and the disease-free survival following salvage mastectomy was 58% at 5 years and 50% at 10 years.[6-10]

All patients with recurrent breast cancer should be considered candidates for one of the ongoing clinical trials testing newly developed chemotherapeutic and biologic agents in phase II studies. For patients with recurrence after an anthracycline-containing regimen, paclitaxel (Taxol) has been approved by the Food and Drug Administration (FDA) for second-line therapy and docetaxel (Taxotere) recently received formal approval by the FDA.

Treatment options:

Standard:

1. If visceral disease is absent and ER and PR status is positive or unknown:
 - Tamoxifen or oophorectomy (or chemical castration with LHRH agonists if surgery cannot be performed) for premenopausal patients. [11,12]
 - Antiestrogen therapy with tamoxifen for postmenopausal patients.
 - Progesterone therapy with megestrol acetate at a dose of 160 mg/day for postmenopausal patients. [13]
 - Aminoglutethimide. [14,15]
2. Surgery and/or radiotherapy if recurrence is localized or visceral. [3,16]
3. Patients who respond to additive hormonal therapy and then relapse should be considered for other forms of hormonal therapy such as those therapies in (1) above not previously used or:
 - Androgen therapy for pre- and postmenopausal patients.
 - Aminoglutethimide.
 - Corticosteroids.
 - LHRH agonists for premenopausal patients.

Selected patients with an initial response to hormone therapy, generally those with soft tissue disease and/or hormone-receptor-positive disease, may have a response to withdrawal of the hormonal therapy of an average duration of ten months, at which time another hormonal therapy can be instituted. [17]

4. If visceral disease is present and ER and PR status is negative:
 - CMF: cyclophosphamide + methotrexate + fluorouracil. [18]
 - CAF: cyclophosphamide + doxorubicin* + fluorouracil. [19]
 - CMFP: cyclophosphamide + methotrexate + fluorouracil + prednisone. [18]
 - CMFVP: cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisone. [19]

The following regimen appears to produce similar outcomes but is in less common use or has been studied less extensively:

CA: cyclophosphamide + doxorubicin*. [20] For patients with recurrence after an anthracycline-containing regimen, paclitaxel has been approved for second-line therapy. Vinorelbine (Navelbine) has also demonstrated activity in patients who relapse after treatment with an anthracycline-containing regimen [21] and has been effective in producing palliation as first- and second-line treatment in advanced breast cancer. [22]

*The potential for doxorubicin-induced cardiotoxicity should be considered in the selection of chemotherapeutic regimens for an individual patient. Recognized risk factors for cardiac toxicity include advanced age, prior chest-wall irradiation, prior anthracycline exposure, hypertension, diabetes, and known underlying heart disease. The cardioprotective drug dexrazoxane (ICRF-187) has been shown in controlled studies to decrease the risk of doxorubicin-induced cardiac toxicity. The use of this agent has permitted patients to receive greater cumulative doses of doxorubicin and allowed patients with

cardiac risk factors to receive doxorubicin. [23,24] The risks of cardiac toxicity may also be reduced by administering doxorubicin as a continuous intravenous infusion. [25]

Under clinical evaluation:

1. If visceral disease is absent, ER and PR status is positive or unknown, and the disease-free interval is long, clinical trials evaluating the role of hormonal therapy such as administration of tamoxifen to premenopausal women should be considered. [11,26,27]
2. For patients with recurrences after an initial response to hormonal manipulation, clinical trials evaluating combination chemotherapy with or without hormonal manipulation or new hormonal therapies should be considered. [27]
3. If visceral disease is present, ER and PR status is negative, or the disease-free interval is less than two years, clinical trials evaluating combination chemotherapy or newly developed chemotherapeutic agents, including paclitaxel, and biologic agents should be considered. [28,29]
4. For metastatic disease, high-dose chemotherapy with autologous bone marrow transplantation has been associated with a high response rate, although responses are generally not of long duration. [30-33] This treatment is under evaluation. Patients considered candidates for this approach should consider enrollment in the PBT-1 trial, a nationwide NCI-sponsored trial comparing high-dose chemotherapy with standard maintenance chemotherapy in patients sensitive to standard chemotherapy. [34]

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FEMALE BREAST CANCER
 Site = C500-509 (740-749); Sex = 2
 Histology = 8000-8231, 8244-8573
 (excludes carcinoids, sarcomas, lymphomas)
 Dxdate >= 1988

*TNM =
4th edition*

74 Group	DEFINITION	CONDITIONS	Rx Group	Rx English
1	STAGE 0 Tis N0 M0 Non-lobular, in situ ¹	Hist=XXXX2X Hist ≠ 8520X	62	R, S
2	STAGE 0 Tis N0 M0 Lobular in situ/ lobular neoplasia	Hist = 85202X	56	H, S Clinical Trials: local exc and Tamoxifen ²
3	STAGE I T1 - N0 M0 ERA Negative	EOD col 1-3 <= 020; 997, 999 EOD col 4-5 = 05, 10, 99 EOD col 6 = 0, 9 ERA = 2	24	C, H, R, S ³
4	STAGE I T1 N0 M0 ERA Positive	EOD col 1-3 <= 020; 997, 999 EOD col 4-5 = 05, 10, 99 EOD col 6 = 0, 9 ERA = 1	24	C, H, R, S ⁴
5	STAGE I T1 N0 M0 ERA Unknown	EOD col 1-3 <= 020; 997, 999 EOD col 4-5 = 05, 10, 99 EOD col 6 = 0, 9 ERA = 0, 3, 8, 9	24	C, H, R, S
6	STAGE II T0, T1, T2 N1 M0 Positive nodes Premenopausal	EOD col 1-3 <= 050 EOD col 4-5 = 10, 99 EOD col 6 = 1-4, 6 Age < 50	24	C, H, R, S
7	STAGE II T0, T1, T2 N1 M0 Positive nodes Postmenopausal	EOD col 1-3 <= 050 EOD col 4-5 = 10, 99 EOD col 6 = 1-4, 6 Age >= 50	24	C, H, R, S
8	STAGE II T2, T3 N0 M0 Negative nodes ERA Negative	EOD col 1-3 > 020 and < 997, 998 EOD col 4-5 = 10, 99 EOD col 6 = 0, 9 ERA = 2	24	C, H, R, S
9	STAGE II T2, T3 N0 M0 Negative nodes ERA Positive	EOD col 1-3 > 020 and < 997, 998 EOD col 4-5 = 10, 99 EOD col 6 = 0, 9 ERA = 1	24	C, H, R, S
10	STAGE II T2, T3 N0 M0 Negative nodes ERA Unknown	EOD col 1-3 > 020 and < 997, 998 EOD col 4-5 = 10, 99 EOD col 6 = 0, 9 ERA = 0, 3, 8, 9	24	C, H, R, S
11	Stage III A T0, T1, T2 N2 M0	EOD col 1-3 <= 050 EOD col 4-5 = 10, 99 EOD col 6 = 5	24	C, H, R, S
12	STAGE III A T3 N1, N2 M0	EOD col 1-3 > 050 and < 997, 998-999 EOD col 4-5 = 10, 99 EOD col 6 = 1-6	24	C, H, R, S
13	STAGE III B T4 any N M0	EOD col 4-5 = 20-70 EOD col 6 = 0-6, 9	24	C, H, R, S
14	STAGE III B any T N3 M0	EOD col 4-5 = 10-70, 99 EOD col 6 = 7	24	C, H, R, S

FEMALE BREAST CANCER
Site = C500-509 (740-749); Sex = 2
Histology = 8000-8231, 8244-8573
(excludes carcinoids, sarcomas, lymphomas)
Dxdate >= 1988

Group	DEFINITION	CONDITIONS	Rx Group	Rx English
15	STAGE IV Any T any N M1 ERA Positive No visceral disease	EOD col 4-5 = 10-80, 99 EOD col 6 = 8 ERA = 1 -----or-----	24	C, H, R, S ⁴
16		EOD col 4-5 = 80 EOD col 6 = 0-7, 9 ERA = 1		
17	STAGE IV Any T any N M1 ERA Negative -----or-----	EOD col 4-5 = 10-80, 99 EOD col 6 = 8 ERA = 2 -----or-----	24	C, H, R, S
18	Visceral disease present (ERA status not a factor; positive and negative included here)	EOD col 4-5 = 85 EOD col 6 = 0-9 ERA = 1, 2		
19	STAGE IV Any T any N M1 ERA Unknown -----	EOD col 4-5 = 80-85 EOD col 6 = 0-9 ERA = 0, 3, 8, 9 -----or-----	24	C, H, R, S
20		EOD col 4-5 = 10-70, 99 EOD col 6 = 8 ERA = 0, 3, 8, 9		
21	STAGE Unknown	EOD col 4-5 = 99 EOD col 6 = 0, 9	24	C, H, R, S

Notes:

TNM staging information is per the AJCC Manual for Staging of Cancer, Fourth Edition. Treatment recommendations are per the PDQ Information for Health Care Professionals, Breast Cancer, modified 1/95. SEER Program Code Manual, Revised June 1992, page 98: Estrogen receptor field (Tumor Marker 1; Section IV, Field 07.A) is coded for breast cases diagnosed on or after January 1, 1990. For all cases diagnosed before January 1, 1990, this field is coded to 9.

- ¹ Although the PDQ specifies ductal carcinoma in situ, the CSS experience shows in situ breast cases that are not ductal (or lobular) are also treated with radiation and surgery. All in situ histologies other than lobular will therefore be queried for radiation and surgery based on the CSS experience.
- ² Clinical trials are evaluating the effectiveness of Tamoxifen after local excision for lobular carcinoma in situ. Approximately 10% of CSS cases of lobular carcinoma in situ receive hormone therapy and approximately 89% are treated with surgery alone. Hormonal therapy will therefore be queried based on the CSS experience.
- ³ The benefits versus risks of hormonal therapy for estrogen receptor negative tumors are discussed at length in the PDQ. Although there is some question as to whether Tamoxifen is of benefit to all due to side effects, approximately 13% of CSS cases with negative lymph nodes and negative estrogen receptors receive hormonal therapy, and approximately 21% of CSS cases with unknown lymph node status and negative estrogen receptors receive hormonal therapy. Hormonal therapy will therefore be queried based on the CSS experience.
- ⁴ The PDQ standard treatment recommendations for cases meeting these definitions include hormonal therapy, radiation and surgery. However, approximately 11% of CSS Stage I, ER positive cases receive chemotherapy and approximately 44% of CSS Stage IV, ER positive cases receive chemotherapy; therefore chemotherapy will be queried based on the CSS experience.

DEPARTMENT OF HEALTH SERVICES

714/744 P STREET

P.O. BOX 942732

SACRAMENTO, CA 94234-7320

(916) 327-4663



Dear Dr. _____:

As you are aware, in 1985 the California Legislature passed Assembly Bill 136 (Sections 215 of the Health and Safety Code) mandating the Department of Health Services to establish a cancer surveillance system to systematically record diagnosis and treatment information on every cancer patient either resident of the state or diagnosed and/or treated within the state. That system has now been in place statewide since 1988 and information on over 600,000 patients have now been recorded.

The primary responsibility of reporting information to the Department is placed on acute care hospitals throughout the state and the majority of cases are reported through this method. However, many patients receive some or all of their treatment outside of acute care hospitals. Thus, we are concerned that we do not have an complete description of the first course of treatment for some of the patients included in our data base. To assess the completeness of our treatment data, we are querying physicians who have diagnosed and/or treated women with early Stage breast cancer since 1991 to determine whether the information currently contained in our data base is complete.

According to our records, your patient, _____ was diagnosed on _____ with stage ____ breast cancer. We would like to know what the complete first course of treatment for this patient was. Could you please complete that information on the attached form and return it to our regional cancer registry using the enclosed envelope.

Your cooperation in this effort is greatly appreciated. These data will be subject to the rules of confidentiality governing the California Cancer Registry. No information which uniquely identifies your patient, yourself, or the facility rendering treatment will be released except under the specific conditions outlined in Health and Safety Code 211.3 and 215 governing research uses of the California Cancer Registry. If you have any questions, please feel free to contact me directly at 916-327-4658.

Sincerely,

John L. Young, Jr., DrPH
Chief, Cancer Surveillance Section

PHYSICIAN'S QUESTIONNAIRE

Patient's Name: ^F2^

CSS No.: ^F1^

Physician: ^F3^ - ^F6^

Date of Initial Diagnosis: ^F4^

Type of Cancer: BREAST

PLEASE INDICATE ALL FIRST COURSE OF CANCER-DIRECTED THERAPY WHICH HAS BEEN GIVEN TO THE PATIENT REGARDLESS OF WHERE IT WAS ADMINISTERED OR BY WHOM. ALSO, WE WOULD APPRECIATE RECEIVING THE LATEST FOLLOW-UP INFORMATION THAT YOU HAVE ON THE PATIENT. THANK YOU.

1. Was this patient registered on a treatment protocol?

☐ 0 No

☐ 1 Yes, protocol sponsor _____
protocol number _____

☐ 2 Is this a local protocol? Yes ☐ No ☐

☐ 7 Patient or patient's guardian refused treatment protocol

☐ 9 Unknown

2. Did this patient receive radiation therapy?

☐ 0 No

☐ 1 Yes, date of first radiation therapy: _____ - _____ - _____
month day year

☐ 7 Patient or patient's guardian refused radiation therapy

☐ 9 Unknown

3. Did this patient receive chemotherapy?

☐ 0 No

☐ 1 Yes, date of first course of chemotherapy: _____ - _____ - _____
month day year

Please check all agents given:

☐ 0 5-Fluorouracil (5-FU)

☐ 1 Cyclophosphamide (Cytosan)

☐ 2 Methotrexate

☐ 3 Doxorubicin (Adriamycin)

☐ 4 Vincristine (Oncovin)

☐ 5 L-PAM, Meiphalen (Alkeran)

☐ 6 Thiotepa

☐ 7 Vinblastine

☐ 8 Other, please specify

☐ 7 Patient or patient's guardian refused chemotherapy

☐ 9 Unknown

4. Did this patient receive hormone therapy?

☐ 0 No

☐ 1 Yes, date of first course hormone therapy: _____ - _____ - _____
month day year

Please check all agents given:

☐ 0 Fluoxymesterone (Halostestin)

☐ 1 Tamoxifen (Nolvadex)

☐ 2 Estrogens

☐ 3 Megestrol Acetate (Megace)

☐ 4 Prednisone/steroids

☐ 5 Aminoglutathimide (Cytadren)

☐ 6 Oophorectomy

☐ 7 Adrenalectomy

☐ 8 Hypophysectomy

☐ 9 Other please specify

(OVER)

- ☐ 7 Patient or patient's guardian refused hormone therapy
☐ 9 Unknown

5. What were the results of the estrogen and progesterone receptor tests?

Estrogen

- ☐ 0 Not done
☐ 1 Positive
☐ 2 Negative
☐ 3 Borderline

Progesterone

- ☐ 0 Not done
☐ 1 Positive
☐ 2 Negative
☐ 3 Borderline

6. Follow-up information

☐ Alive Date of last contact _____
☐ Dead Date of Death _____

County/State of Death _____

7. If you believe this information to be incomplete, are there other physicians we could contact who may have further information on this patient?

Dr. _____ Address _____

Dr. _____ Address _____

Physician Signature _____ Date _____

MARK E. ALLEN
 9501 Laguna Lake Way
 Elk Grove, California 95728
 (916)684-3079

QUALIFICATIONS: Proven leader, organizer, personnel manager, production manager.

EDUCATION

M.S., With Distinction, in Operations Research, Naval Postgraduate School, Monterey, California (1974-1976)

M.S. in Aeronautical Systems, University of West Florida (1969-1970)

Naval War College, Newport, Rhode Island (1979-1980)

Lehigh University, Mathematics, 12 graduate credits (1968)

B.S. in Mathematics, University of California, Davis (1964-1968)

PROFESSIONAL AFFILIATION

Sigma Xi, The Scientific Research Society of America

EMPLOYMENT

Mathematics Instructor, University of the Pacific 8/90 to present. Courses:

-**Statistics** (descriptive statistics, probability theory, hypothesis testing, confidence intervals, linear regression, analysis of variance, nonparametric methods). Computer applications using SPSS and SYSTAT.

-**Topics in Operations Research** (linear programming, network theory, nonlinear programming, markov chains, queuing theory and forecasting).

-**Calculus for Decision Makers** (functions, limits, differentiation, curve sketching, maxima and minima problems, approximation of functions, integration, numerical integration). Computer applications using LOTUS 123 and QUATTRO PRO.

Mathematics Instructor, Cosumnes River College 8/89 to present and American River College 1/90 to present (part-time). Courses:

-**Statistics** (descriptive statistics, probability theory, hypothesis testing, confidence intervals, linear regression, analysis of variance, nonparametric methods). Computer applications using MINITAB.

-**Engineering Calculus** (functions, limits, differentiation, curve sketching, maxima and minima problems, approximation of functions, integration, numerical integration, volumes of revolution, surface area, moments, computer applications).

Mathematics and Management Science Instructor, National University and Golden Gate University 7/89 to 1/91 (part-time). Courses (all taught in computer classrooms):

- Inferential **Statistics** (hypothesis testing, regression analysis and times series analysis)
- Business Mathematics (review of algebra, matrix algebra and differential calculus).
- Methods of **Operations Research** (decision theory, linear programming, network theory and queuing theory).

US Navy, 1/69 to 5/89

BATTLE GROUP COMMANDER'S STAFF, 5/87 to 5/89

-Developed prototype **computer command and control** data base management system for the battle group command center. The system consisted of thirty-two computers networked together to provide real time locating and targeting data on air, surface and subsurface contacts as well as decision aids and planning tools for staff members. Gave daily **briefings** on the status of battle group command and control.

-Personally **organized** the division of responsibilities of the command center and **trained** staff personnel in the functioning and utilization of the command and control system.

-**Planned** and conducted three successful major exercises with allied navies and air forces that were each an "unqualified success as noted by Commander Seventh Fleet and Commander Task Force Seventy".

NAVAL AVIATION SQUADRON POSITIONS 1970-1987

- Served as **Pilot and Aircraft Commander** in four squadrons that flew the E-2C "Hawkeye" airborne early warning aircraft from various aircraft carriers operating in the Pacific Ocean and the Persian Gulf region.

- Assumed increasingly responsible administrative positions, first as a division officer, then as a department head, culminating in a squadron tour as **Executive Officer** and **Commanding Officer**. While Executive and Commanding Officer, won all awards available to a squadron including designation as the best E-2C squadron in the Navy. **Scheduled** aircrews to meet operational commitments and maximize operational readiness within the constraints of a limited budget. **Managed** a department of nearly one hundred technicians and mechanics and coordinated and prioritized the repair and upkeep of aircraft. **Supervised** staff responsible for providing personnel services and maintaining all squadron and personnel records. As **instructor** pilot in all four squadrons, trained junior pilots and each year tested all pilots for qualification for continued flying.

**IMPROVING THE USEFULNESS OF
THE CALIFORNIA CANCER REGISTRY DATA ON BREAST CANCER
BY LINKING WITH HOSPITAL DISCHARGE RECORDS**

**CANCER SURVEILLANCE SECTION
CALIFORNIA DEPARTMENT OF HEALTH SERVICES**

William E. Wright, Ph.D.
Chief, Research and Surveillance Program
Cancer Surveillance Section

John L. Young, Jr., Dr.P.H.
Chief, Cancer Surveillance Section

November 9, 1995

IMPROVING THE USEFULNESS OF THE CALIFORNIA CANCER REGISTRY DATA ON BREAST CANCER BY LINKING WITH HOSPITAL DISCHARGE RECORDS

1. SUMMARY OF THE NATURE AND GOALS OF THE STUDY

The California Cancer Registry (CCR) was established in order ". . . to determine the sources of malignant neoplasms and evaluate measures designed to eliminate, alleviate, or ameliorate their effect" (Health & Safety Code Section 211.3(g)). Beginning with 1988, all malignant cancers (with the exception of basal and squamous cell carcinomas of the skin) that are diagnosed in the state are reportable to the CCR. In 1993, the most recent year for which case reporting is at least 95% complete, over 120,000 cases were reported. The Cancer Surveillance Section (CSS) routinely monitors the completeness and quality of the data that are reported to the CCR, and conducts research on both suspected causes and treatment patterns among cancer victims.

The CSS is proposing to conduct four studies of female breast cancer which will involve linking California Hospital Discharge Data (CHDD) containing personal identifiers to the CCR records. These studies are:

- (1) Case Reporting. The first study is a quality control study of the completeness of the CCR database which involves verification of the CCR case-finding. The CCR relies on hospitals to report cancer cases to it through our ten Regional Registries. If the CHDD contains breast cancer cases that are not known to the CCR, then this linkage should uncover those cases.
- (2) Treatment Data. The second study is a more complete assessment of treatment for breast cancer. Hospitals are requested to report the first course of treatment only which is usually treatment that is delivered within the first six months following diagnosis. This study would allow us to examine treatment that is reported to the CCR within the first six months of diagnosis compared with treatment information over a longer time period contained in the CHDD.
- (3) Followup. The third study involves followup on previously diagnosed cases. Part of the CCR's mission is to calculate survival following diagnosis and treatment for cancer. Because of budget cuts during the past few years, this function has not been completely implemented, and we only perform an annual linkage with California death certificates to assess vital status. Linkage with the CHDD database would allow us to improve followup. For example, a breast cancer patient diagnosed in 1988 who is subsequently hospitalized in 1993 would be "known to be alive" in 1993 rather than "lost for followup".

- (4) Comorbidities. The fourth study involves an assessment of comorbidities among breast cancer patients. The CSS is currently examining treatment that women receive following a diagnosis of breast cancer. Certain treatments, e.g. radiation therapy, may be contra-indicated depending on patient comorbidities. However, the CCR does not collect comorbidity data. Linkage with the CHDD will allow for a more complete analysis of breast cancer treatment patterns in California controlling for comorbidities.

Beginning on July 1, 1990 the Office of Statewide Health Planning and Development (OSHPD) began collecting hospital discharge abstract records with patient social security numbers. Through an interdepartmental agreement, the OSHPD makes these data available to the Department of Health Services (DHS) where they reside in the Center for Health Statistics, Planning and Data Analysis Section. The policy governing access to the non-public portions of these records require that all research protocols be approved by the Health and Welfare Agency Committee for the Protection of Human Subjects.

The CSS is requesting access to CHDD Confidential Data Set for all female California residents (excluding patients under the age of 20 and all pregnancy related discharges) for the time period January 1, 1991 through December 31, 1994 and to their diagnostic, treatment, demographic, and expected cost data. All linkage activities will be performed by CSS staff on CSS equipment in secure conditions under procedures governing the confidentiality of cancer case reports (Health and Safety Code 211.3, 211.5, and 215). At present time, the CCR database contains well over one million records dating back to 1973. To our knowledge, there has never been a violation of the confidentiality of our records.

This linkage project is a part of our workplan for a project funded by the Department of the Army (California Cancer Registry Enhancement for Breast Cancer Research, U.S. Army Medical Research Acquisition Activity, Grant No. DAMD17-94-J-4508). It is also a part of our activities mandated by AB 478, the Breast Cancer Act of 1993 (Friedman), and it is a deliverable product of the California Health Information for Policy Project (CHIPPP) funded by the Robert Wood Johnson Foundation to the Office of Statewide Planning and Development.

2. DESCRIPTION OF HUMAN SUBJECTS INVOLVED IN THE STUDY

The project will only involve linking records of female breast cancer cases diagnosed between 1988 and 1993 with hospital discharge records for 1991-1994 for all women over the age of 19. Minors will be excluded because of the rarity of breast cancer among minor females (less than five cases total for the five years 1988-1992). Women with pregnancy related hospitalizations will be excluded in order to reduce the size of the discharge file and make it more manageable for linking purposes.

3. DESCRIPTION OF THE USE OF HUMAN SUBJECTS

This project will not directly use human subjects; only their preexisting records will be involved.

4. ASSESSMENT OF POTENTIAL BENEFITS

There are no immediate benefits to the women whose records will be linked in this study. Long-term benefits may accrue to California women if the linkages yield valuable data to further the study of breast cancer and its treatment.

5. ASSESSMENT OF POTENTIAL RISKS

There are no risks to the women whose records will be studied other than a remote possibility for a breach of confidentiality.

6. DESCRIPTION OF MEASURES TAKEN TO MINIMIZE POTENTIAL RISKS

The CCR and CHDD data files and access to them will be maintained under mandates provided by Health and Safety Code Sections 211.3 and 211.5. The electronic data files with personal identifiers will be maintained in locked files at the offices of the DHS Cancer Surveillance Section (CSS). Only approved scientific investigators will have access to the confidential portions of the data files. There are no known breaches of confidentiality in the history of the CSS which currently contains over 1.5 million records.

7. OBTAINING AND DOCUMENTING INFORMED CONSENT OF THE SUBJECT

There is no provision for obtaining informed consent for this project.

8. DESCRIPTION OF MEDICAL SERVICES PROVIDED TO SUBJECTS

No medical services will be provided.

9. JUSTIFICATION FOR WAIVER OF WRITTEN INFORMED CONSENT

A waiver of the requirement for written informed consent is sought for the following reasons:

- a. The project will be conducted by state government officials under the authority of Health and Safety Code Section 211.3.
- b. The CCR database contains a patient's address of record at the time of diagnosis. (The CHDD does not contain name or address.) These addresses are not updated routinely. The costs to search out breast cancer patients (114,019 for the time period 1988-1993) and obtain written informed consent is prohibitive.
- c. The risks of potential harm to the subjects is minimal.
- d. The waiver will not adversely affect the rights and welfare of the subjects.

10. QUESTIONNAIRE OR INTERVIEW SCHEDULES

This project will not involve questionnaires or interviews.

11. SPECIAL OR UNUSUAL CIRCUMSTANCES

None.

12. DOCUMENTATION ALLOWING TESTING OF A NEW DRUG OR DEVICE

Not applicable.

13. SIGNATURES OF PRINCIPAL INVESTIGATOR AND RESPONSIBLE OFFICIAL

Signatures of the Principal Investigator and a Responsible Official of the Institution, indicating assurance of compliance with the U.S. Department of Health and Human Services (DHHS) Regulations for the Protection of Human Subjects.

We agree to comply with and be bound by the U.S. DHHS Regulations for the Protection of Human Subjects and relevant ethical principles. We agree to comply with and be bound by all Health and Welfare Agency Committee for the Protection of Human Subjects decisions.

Signature: William E. Wright

Signature: Donald O. Lyman

Name: William E. Wright

Name: Donald O. Lyman

Title: Chief, Research and

Title: Chief, Chronic Disease

Title: Surveillance Program

Title: and Injury Control

Date: November 9, 1995

Date: November 9, 1995

14. ADDRESS AND TELEPHONE NUMBER OF PRINCIPAL INVESTIGATOR AND CURRICULUM VITA

William E. Wright, Ph.D.
Department of Health Services
Cancer Surveillance Section
601 N. 7th Street/MS#592
Sacramento, CA 94234-7320

Phone: (916) 322-5863

Fax: (916) 327-4657

Curriculum Vita (Attached)

15. PROJECT BUDGET AND SOURCE OF FUNDING

This study is supported by funds to the California Cancer Registry from the Department of the Army (California Cancer Registry Enhancement for Breast Cancer Research, U.S. Army medical Research Acquisition Activity, Grant No. DAMD17-94-J-4508).